



Large local reactions to insect envenomation

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Purpose of review

Insect stings often induce large local reactions (LLRs) that result in morbidity. These reactions do have an immunologic basis; however, patients presenting with LLRs should be managed differently than those with systemic allergic reactions, as described in this review.

Recent findings

Morbidity results from the inflammation itself along with the iatrogenic consequences of treatment. The prescription of antihistamine medications and the use of antibiotics are generally not indicated for patients with LLRs because of the risks/side-effects of these medications and the low probability of benefit. Some patients are also concerned over the possibility that a future sting will evolve into a life-threatening reaction. Although these reactions do involve IgE, patients are not at sufficient risk to warrant prescription of autoinjectable epinephrine. Venom-specific immunotherapy can be considered when LLRs are frequent and associated with significant impairment.

Summary

Clinicians can reduce morbidity from LLRs by reassuring the patients, avoiding medications that result in side-effects when they are not indicated, and referring to an allergist when there are additional concerns, such as frequent impairment.

Keywords

allergy, hymenoptera, immunotherapy, insect sting, large local reaction, venom

INTRODUCTION

Social species of Hymenoptera sting in self-defense or in defense of their colony. They are often brightly colored to warn mammals away; however, antagonistic interactions with humans are common. Immediate-type local allergic reactions can be difficult to distinguish from the direct toxic effects of Hymenoptera venom in part because of the neuropeptides and proinflammatory compounds in the venom [1]. Pain is out of proportion to the physical damage of the venom, but inflammation of the tissues is prominent. The direct effects of the venom peak within an hour, and then begin to fade, although full healing may take days or weeks. Some people may have local induration that is more pronounced and more prolonged than usual. These nonallergic local reactions increase gradually from the time of the sting and may take days to subside. Many such individuals give a history of similarly unusual large local reactions (LLRs) to various insect bites.

After the effects of the toxins have peaked, some patients will develop large local immunologic reactions. LLRs following insect stings are common, with most prevalence estimates ranging between 5 and 15%. These reactions usually begin 6–12 h

after a sting, suggestive of a late-phase reaction in response to mast cell activation. The reactions peak at 24–48 h, and then subside in 5–10 days. Patients having acute LLRs often come to the attention of physicians because there is marked discomfort and/or physical limitation because of the local inflammation, and because extreme swelling can be frightening especially when there are lymphangitic streaks spreading proximally from the site of the reaction. Patients who have had LLRs to stings may seek medical advice because the reactions cause anxiety about the potential risk for anaphylaxis with subsequent stings. This review will address these issues and the debate about whether to administer venom immunotherapy (VIT) for these concerns.

LLRs represent an IgE-dependent late-phase allergic inflammatory process that probably involves T-lymphocytes as well as other inflammatory cells

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KEY POINTS

- Management of LLRs from Hymenoptera stings can include NSAIDs, cold compresses, and corticosteroids; antihistamine medications and antibiotics should generally be avoided.
- Although IgE-mediated, LLRs infrequently progress into life-threatening systemic reactions, and autoinjectable epinephrine is not usually prescribed.
- For patients with recurrent LLRs and significant morbidity, venom-specific immunotherapy should be considered.

and cytokines [2,3]. About 75% of patients who have had LLRs have venom-specific IgE on skin tests or serum tests [4–7]. This is similar to the proportion of patients with systemic reactions who have positive tests for venom-IgE. Because LLRs develop more than 6 h after stings and are IgE-mediated, they are suspected to be late-phase reactions. Late-phase reactions in the skin are attributed to the transcription of newly formed mediators by mast cells after degranulation. These newly formed mediators include cytokines and chemokines that promote the influx and activation of lymphocytes, eosinophils and other cells into the tissue. This results in substantial inflammation that can exceed the inflammation seen in early phases of immediate-type reactions.

MORBIDITY (HOW BAD CAN IT BE?)

There is no standard definition of a LLR; however, inflammation greater than 10 cm is a common cutoff. The impairment caused by these reactions ranges from mild distraction to functional limitations in the part of the body that was stung, particularly when the reaction includes a distal extremity or the face. The degree to which these reactions cause impairment or discomfort may be as much related to the site of the sting as the size of the reaction. In some locations, a LLR could cause a compartment syndrome that can compress nerves, muscles, or blood vessels.

Morbidity is also caused through the treatment of LLRs. Side-effects from antihistamine medications include cognitive impairment that increases the probability of motor vehicle crashes [8], and more recently, the link between cumulative use of anticholinergic medications and dementia has been supported [9]. Because the late-phase and delayed-type mediators typically affect histamine-insensitive itch pathways, rather than histamine-sensitive c-fibers, these medications are unlikely to be effective, and

should be avoided. Alternatives include application of ice or cold compresses and use of NSAIDs to treat inflammation and pain, if needed.

In contrast to antihistamine medications, the eosinophils and T-lymphocytes involved in late-phase reactions are theoretically responsive to corticosteroids although controlled studies that examine the effects when used after stings are lacking. The short-term and long-term effects of systemic corticosteroids are of concern, but may be justified when there are significant limitations in function. Topical application of corticosteroids can be considered in treatment although there have been no studies to determine whether they provide significant benefit.

Lastly, the inflamed area and the inflammatory lymphangitis seen in many patients with LLRs are commonly mistaken for an infectious cause and inappropriately treated with antibiotics, thus introducing additional potential adverse effects. Infection at the site of an insect sting is quite unusual, and would likely take several days (not 24 h) to become severe.

The morbidity from LLRs can be significant with each sting, but patients with recurrent stings can expect repeated morbidity. Individuals with a history of LLR have a very high frequency of another LLR to subsequent stings. In a sting challenge study [10] of large local reactors, 40 of 41 study participants had another LLR.

ANXIETY (HOW MUCH SHOULD I WORRY?)

The anxiety that some patients feel about LLRs may be initiated by friends and even physicians concerned about the risk of fatal systemic reactions to subsequent stings ('the next one will kill you'). In fact, the risk of anaphylaxis with subsequent stings in those with LLRs appears to be lower than asymptotically sensitized patients in the general population, who have a 5–15% probability of having a systemic reaction [11,12[■]]. There have been several studies reporting on the frequency of systemic reaction in patients with a history of LLR, but all of them studied very small numbers of patients and most of them were retrospective. The incidence of systemic reactions to stings in patients with LLRs has generally been reported to be in the range of 4–10% [6,7,10,13]. In two other studies [14,15[■]], there were no systemic reactions to stings in patients with a history of LLR (in 23 and 31 patients, respectively). Pucci *et al.* [15[■]] suggest that patients who have had two or more LLRs are very unlikely to have a systemic reaction to a subsequent sting. In a large study [16] of children, 5644 of whom had been

stung at least once, there was a statistical association of LLR and systemic reaction, but it was not clear how many had LLR prior to systemic reaction (as opposed to those who had LLR during or after systemic reaction to stings). They also reported that the frequency of both LLR and systemic reaction was correlated with the number of times the study participants had been stung. Most of the systemic reactions that occur in patients with prior LLR are not severe, so the risk of anaphylaxis requiring emergency treatment in large local reactors is probably less than 3%. In a sting challenge study [10] of patients with LLR, one of 41 had a systemic reaction but it caused very severe and prolonged anaphylaxis. Unfortunately, there is no test that can predict which of these individuals will have an anaphylactic reaction to a sting. On the other hand, patients who have had LLRs are very likely to have another LLR to a future sting. In a sting challenge study [10] of large local reactors, 40 of 41 patients had another LLR. This can justify the early use of oral corticosteroids to help abort or minimize the local inflammatory reaction, and can justify the recommendation of VIT to patients who are likely to be stung every year.

Although the risk of a systemic reaction is greater in the patient with LLR versus the general population in which sensitization status is unknown, the prescription of autoinjectable epinephrine is not generally indicated because of the very low risk. Venom allergy testing may confuse rather than clarify risks because they can be positive in 40% of people who have been recently stung [11], and have relatively poor positive predictive value. Referral to an allergist should be made if autoinjectable epinephrine or allergy testing is considered, or simply to provide the patient with the most appropriate expert information and advice [17].

An important role of mast cells appears to be detoxification and localization of venom responses, with mast cells preventing mortality from honey bee venom in mice [18]. Indeed the proteases released locally into envenomated tissue may be adaptive, and represent an appropriate immunologic reaction to venom. The differences in patients that have systemic versus local reactions may provide insight into normal and abnormal allergic responses and warrant further study.

An elevated baseline serum tryptase can be seen in patients with mastocytosis and other conditions, and identifies a group of patients more likely to have severe reactions to venom through immunologic and nonimmunologic triggers [19]. Although an elevated baseline tryptase may suggest that the patient is more likely to have a systemic reaction to venom in general, this has not been examined specifically in patients with LLRs. Measurement of

baseline serum tryptase is not recommended in patients with LLRs.

AUTOINJECTABLE EPINEPHRINE (DO I REALLY NEED IT?)

The anxiety experienced by those with venom allergy may be worsened when physicians prescribe autoinjectable epinephrine [20,21]. Cautious physicians, recognizing that an IgE-mediated reaction is responsible for these LLRs sometimes prescribe autoinjectable epinephrine because of the perceived risk of anaphylaxis with subsequent stings. Current consensus is not to prescribe autoinjectable epinephrine in a patient without systemic allergic reactions, even when IgE is present, unless there are other risk factors involved. A discussion with an allergist is warranted in those cases because there is currently no consensus on what level of risk warrants prescription of autoinjectable epinephrine. For example, many allergists do prescribe autoinjectable epinephrine to patients on VIT despite having a very low probability of reaction. This sends a mixed and perhaps inappropriate message that VIT gives excellent protection but the patient should still carry epinephrine. Similarly, epinephrine prescription to patients with LLRs gives patients the impression that there is significant risk of anaphylaxis, even when they are told that the risk is 'minimal'. Prescription of epinephrine is not benign and is associated with impaired quality of life [21–23].

VENOM IMMUNOTHERAPY (IS IT WORTHWHILE?)

As noted above, VIT greatly reduces the probability of systemic allergic reactions in patients with a previous history of systemic reactions, and would certainly do the same in large local reactors. In addition, venom-specific immunotherapy can also reduce the size and duration of LLRs [10]. In one study [24], sublingual VIT showed limited effectiveness in the first summer of treatment, but there was no report of the outcome of continued maintenance immunotherapy. There is also concern about the potential for airway edema and obstruction if venom is given by the sublingual route [25]. Careful consideration must be given to starting immunotherapy for LLRs because with any immunotherapy there is a risk of systemic reaction to the injections. However, in the study of subcutaneous VIT there were no systemic reactions reported, and there were minimal problems with LLRs to VIT. Therefore immunotherapy can be considered in patients for whom stings are frequent and associated with significant morbidity. In such cases, VIT

may also be viewed as a steroid-sparing treatment because these patients are often treated with oral corticosteroids, sometimes more than once each summer.

CONCLUSION

LLRs are IgE-dependent immunologic responses to venom that begin hours after envenomation, increase over 1–2 days, and may take a week or more to resolve. The morbidity from these reactions depends on the size and location of the sting, along with the side-effects of the medications that may be inappropriately used to treat the reactions. Concern over the possibility of systemic reactions with subsequent stings is generally not sufficient to warrant prescription of autoinjectable epinephrine or immunotherapy, and allergy testing is not generally indicated. However, VIT may be considered in patients with frequent and unavoidable stings that cause severe LLRs. When concern remains, referral to an allergist can be made to review the risks of future stings and options for treatment and prevention.

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