Large Local Reactions to Insect Stings

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Large local reactions (LLRs) are IgE-mediated late-phase inflammatory reactions that can cause great morbidity but are associated with a relatively low risk of future anaphylaxis. Patients with LLR may benefit from consultation with an allergist to help clarify the relative risk, to plan the best treatment for future stings, and to determine whether or not to pursue testing or venom immunotherapy (VIT). The chance of anaphylaxis to future stings is <5%, so VIT is not generally recommended to people who have had LLR. Whether to prescribe an epinephrine injector is often determined by the frequency of exposure, the proximity to medical care, and the impact on quality of life. For people who have unavoidable exposure and need treatment almost every year for LLR, VIT can be recommended with confidence that it will significantly and safely reduce the severity of LLR to stings. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:331-4)

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Insect stings normally cause local itching, burning, and swelling that subside in hours. These normal reactions are usually not more than 2-3 cm in diameter and have minimal or mild local induration that might persist for a few days. Some individuals get larger than usual swelling from a variety of insect bites and stings, which represents a nonallergic irritability of the skin. Allergic reactions to stings can be local or systemic. Systemic, or anaphylactic, reactions have been reviewed elsewhere, and have been the main focus of research and clinical efforts for diagnosis and treatment.[1] Local reactions can be much larger and more prolonged when they are allergic. Some people get immediate severe swelling, but the typical large local reaction (LLR) to a sting is minimal in the first few hours, which increases 6 hours or more after the sting, progresses for 24-48 hours, and subsides after 5-10 days or longer. The size of an allergic LLR has not been specifically defined, but is usually more than 10 cm in diameter, often 15-20 cm, and can occasionally cause massive swelling of an entire limb. On the extremities, LLRs are often associated with the appearance of lymphangitic streaks toward the axillary or inguinal lymph nodes. These are usually interpreted by urgent care physicians as signs of cellulitis, but this is never the case only 24-48 hours after a sting; they represent inflammatory, rather than infectious, lymphangitis. Although the morbidity of LLR is substantial, there is no danger unless the swelling causes compression in a limited space (compartment syndrome), or is located at the site of a sting in the oropharyngeal airway. Because the swelling develops gradually, these dangers are subacute in nature, usually allowing adequate time for medical evaluation and treatment.

EPIDEMIOLOGY

The epidemiology of LLR is not as well studied as that of systemic reactions. It is likely that the frequency of LLR is the same as or greater than that of systemic sting reactions. Systemic reactions have occurred in less than 1% of children and in approximately 3% of adults surveyed. The prevalence of LLR varies widely in published estimates. There are few data on children, but a study of Italian school children found a prevalence of LLR of 19%.[2] A study of 10,000 Israeli high school students found that 11.5% reported LLR.[3] Studies of adult populations report a wide range of prevalence of LLR between 4.6% and 26.4%, with most studies in the range of 5% to 15%.[3-6] The variation in these reports is due to a number of factors including the frequency of insect stings in the population, the age of the subjects studied (children vs adults), the definition of LLR that was used, and the recall bias of the subjects surveyed (the size of the LLR, like that of the last fish they caught, often being exaggerated in retrospect). Some studies have included swellings of just 5 cm as LLR. The frequency of stings is certainly a risk factor for sensitization as well as allergic reactions. Two studies on beekeepers reported the frequency of LLR to be 12%[7] and 38%.[8]

IMMUNOLOGICAL OBSERVATIONS IN LLR

The mechanism of LLR is most likely that of IgE-dependent late-phase inflammatory reactions. The LLR resembles the "late cutaneous allergic response," as described by Umemoto, and the "late-phase reaction," as studied by Solley.[9,10] Most studies find positive venom skin tests or serum IgE tests in 70% to 80% of LLR, which is similar to the observations in patients with insect sting anaphylaxis.[7,11-14] Some studies have found less than 50% of LLR to have venom-IgE, but they were often limited to puncture skin tests (not intradermal) or serum IgE only, or may have reflected LLRs that were relatively small in size (which may not be allergic).[2,4]

RISKS ASSOCIATED WITH A HISTORY OF LLR

A history of previous LLR can be of little concern in some people and much more in others. For most people, the LLR is a

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rare occurrence because they are rarely stung (once every 10-30 years). For other people, it presents a greater concern that is often related to the frequency of exposure to stings. For those who work outdoors or participate in outdoor activities with frequent exposure to stinging insects, it is not uncommon to have several incidents each summer that are associated with morbidity, the need for medical attention, and often a course of corticosteroid medication (or, mistakenly, antibiotics). Although not studied in patients with large local reactions, the quality of life is impaired in patients who have only cutaneous systemic reactions.[15] The greatest risk in patients with LLR is of local airway obstruction associated with a sting in the oropharynx.

NATURAL HISTORY AND PROGNOSIS IN PATIENTS WITH LLR

The outcome of subsequent stings in people who have had LLR has been studied prospectively and retrospectively. Unfortunately, people often hear dire predictions from doctors, friends, and relatives who say "the next one could kill you." Considering that patients with LLR often have venom-IgE (or skin test) results similar to those in patients with anaphylaxis, they have a surprisingly low incidence of systemic reactions to stings, in the range of 4% to 10%.[12,13,16,17] In a 15- to 20-year follow-up survey of children, those with a history of LLR had a 7% incidence of a systemic reaction.[16] However, in a retrospective survey of 10,000 high school students, those who had a systemic reaction to a sting had a higher frequency of previous LLR than the students with no history of a systemic reaction.[3] So, although it is associated with a chance of a systemic reaction about twice that of the general population, a history of LLR carries a risk of anaphylaxis lower than in all other sensitized individuals. For example, even people with asymptomatic sensitization (positive tests for venom-IgE but no history of an allergic reaction to a sting), constituting up to 15% of adults, have a 10% to 15% chance of a systemic reaction to a future sting, which is twice that of large local reactors, who have similar venom-IgE or skin test sensitivity.[18] On the other hand, individuals with a history of LLR have a very high frequency of another LLR to subsequent stings. In a sting challenge study of large local reactors, 40 of 41 subjects had another LLR.[17] It is intriguing to wonder why large local reactors, who have the same venom-specific IgE as systemic reactors, so rarely have systemic reactions to stings. In this respect, insect sting allergy is a useful model for the larger question of what distinguishes those with asymptomatic sensitization from those with seemingly identical allergy who have severe reactions. The most attractive hypothesis relates to intrinsic pathways of basophil responsiveness. This is supported by preliminary evidence that the basophil activation test can distinguish patients with peanut allergy from those with asymptomatic sensitization.[19]

There is an element of medicolegal risk in the counseling of patients with LLR. It is not cost-effective to recommend treatment when there is a more than 95% chance that it is not needed. However, there is no test that distinguishes those who will have a systemic reaction from those who will not. The significance of a 4% to 10% chance of a systemic reaction, only some of which will be severe enough to require epinephrine treatment, will be different to different individuals. This requires patient-physician discussion to achieve a treatment plan that is appropriate for the comfort level of the patient and the clinical judgment of the physician.

DIAGNOSTIC EVALUATION

The approach to diagnosis and management is shown in the algorithm in Figure 1. Perhaps the first question, for the patient, the primary doctor, and the allergist, is whether people with LLR should be evaluated by an allergist. The main reason for referral to an allergist in such cases is to get accurate informed discussion about the relative risk of future reactions and the utility of diagnostic testing or specific treatment. This will often help to avoid unnecessary impairment of quality of life, and unnecessary testing and treatment, but will also help to identify those who would benefit from testing and treatment. The majority of people with LLR do not require testing or venom immunotherapy, because the chance of anaphylaxis to a future sting is acceptably small.

It is important to recognize the reasons for not performing the diagnostic tests. They are always performed in the hope that they will be negative, which will reassure the patient and eliminate the need for treatment. However, the tests are positive in approximately 20% of normal adults, and in almost 40% of those who have been recently stung (without an allergic reaction). Such asymptomatic sensitization carries very low risk of future anaphylaxis, much like the situation in large local reactors. So when diagnostic venom tests are ordered in "low-risk" patients such as large local reactors, there is a very high chance that the test will be positive but of little clinical value.[20] There is currently no diagnostic test that can distinguish which of these individuals will ultimately have a systemic reaction to sting. There is preliminary evidence that basophil activation tests may distinguish those patients who remain reactive to stings despite venom immunotherapy (VIT).[21,22]

PREVENTION AND TREATMENT

Treatment of the acute LLR is symptomatic. If a stinger is present in the skin, it should be scraped (not squeezed) to remove it as soon as possible. Local application of ice or cold compresses may be helpful initially. Antihistamines will help the itching more than the inflammatory induration. Moderate reactions do not require additional treatment, and there is almost never a need for antibiotics. Severe large local reactions are often treated with oral corticosteroids for a few days, but it is believed to be more effective to begin the steroids as soon as possible after the sting so as to prevent the late-phase inflammatory response.

Prevention of reactions can include avoidance precautions, but it is always preferred to avoid disrupting normal activities. Patients should be warned to avoid eating or drinking outdoors, and to particularly avoid drinking from straws or beverage containers where yellow jackets often lurk. Prevention of severe or dangerous systemic reactions may also include prescription of an epinephrine autoinjector, with education and training on its proper use, and when to use it or not use it. However, it has been shown that simply prescribing an epinephrine injector does not improve quality of life, because patients are still fearful of stings and potential reactions.[15,23,24] The need to prescribe an epinephrine injector has been questioned because it is not cost-effective, and it sends a "mixed message" to the patient or family that the risk is low (not requiring VIT) but they should carry the epinephrine injector because they could have a dangerous reaction. The frequency of exposure, the distance from emergency medical care, and the patient's personal preference will help to decide on whether to prescribe epinephrine.

A history of LLR is not normally an indication for VIT.[25] It has been judged to be not cost-effective to treat patients