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RESEARCH LETTER

Patient History Is Often Reliable in Cases of Venom-Induced Anaphylaxis: A Retrospective Observational Study

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For patients that have experienced a systemic allergic reaction induced by Hymenoptera venom, venom immunotherapy (VIT) dramatically reduces the risk of subsequent reactions.[1] Similarly, whole body extracts (WBE) are used in immunotherapy for Solenopsis (fire ant) species allergy with improvements in prognosis comparable to VIT.[2] Among the barriers to diagnosis and management of insect hypersensitivity is the need for allergy testing for the selection of immunotherapy extracts prior to immunotherapy.[3] Testing is generally performed after a theoretical 6-week refractory period following an anaphylactic event, by an allergist that performs and interprets venom allergy testing varies. Testing options include skin and serum tests, with current guidelines recommending skin testing followed by serum testing when results are negative. At some centers, the order of testing has been reversed for reasons that include time constraints and costs that limit skin testing along with increased sensitivity of serum testing.

Allergists rely on venom allergy testing to help select the appropriate extracts for use in desensitization. Allergists may be hesitant to narrow the scope of testing based on patient history. This hesitance stems from a single study, which questioned the reliability of patient-reported information concerning insect taxonomy. It is worth noting that this study primarily considered patient knowledge of insects rather than the expertise of physicians in interpreting patient history.[4]

Current guidelines do recognize the potential of history-based approaches, particularly when the identity of the offending insect is unequivocal.[5] For instance, the presence of a sterile pustule following a sting is widely regarded as pathognomonic for fire ant stings. In cases where expert identification of the insect is feasible, such as when a specimen is brought in by the patient, this further supports restricting the scope of venom allergy testing. Allergists that infrequently perform venom immunotherapy may be unaware of the relative usefulness of history elements in selecting venom extracts for testing and desensitization. Our study was conducted to determine how often elements of the history could be used to restrict the number of taxa for which patients were desensitized in a referral center for patients with venom-induced anaphylaxis.

After approval by the Ochsner health system IRB with a waiver of informed consent due to minimal risk, we conducted a retrospective chart review of 52 patients who initiated VIT with an ultrarush induction protocol at our New Orleans center from 2016 to 2022. Patients were identified using CPT codes (9513X, 9514X, or 95170) indicating immunotherapy with Hymenoptera venom extracts or fire ant WBE. All patients who underwent ultrarush were included, with no patients excluded.

The time elapsed between the initial anaphylactic reaction and the initiation of immunotherapy was determined. For adult patients with a history of reaction in childhood (without specified age), the date the patient turned 18 years old was assigned. When only a year was documented in the patient's chart, the last date of the year was used.

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Patient history was examined for elements used for extract selection. Elements used for implicating are listed in Table 1. When history implicated an insect, testing results were analyzed to determine concordance between history, testing results, and final extract used for desensitization.

All patients (N = 52) who underwent the ultrarush procedure were included, with no patients excluded. Demographic data based on self-reported sex revealed that 58% of patients were female (N = 30), while 42% were male (N = 22). The study comprised 29% pediatric patients (18 years old or younger at the time of the ultrarush procedure) and 71% adult patients. Regarding race, 75% of patients identified as White (N = 39), 13% as Black (N = 7), 4% as Native American (N = 2), 2% as Asian (N = 1), 2% as Mixed (N = 1), 2% as Other (N = 1), and 2% did not report their race (N = 1).

Our results showed that the average delay between an anaphylactic event and venom immunotherapy initiation was 1,018 days (range = 24 days to 37.6 years; SD = 2,831 days), but this decreased to 344 days when three outliers were excluded. Patient history was useful in identifying the insect genus in 73% of cases (38 of 52 patients) (see Table 1). It is important to note that, for 50% of cases, history implicated fire ants (N = 26). Reliable history elements for fire ant identification included witnessing ant stings (N = 13), the presence of a pustule 24 hours post-event (N = 5), or a combination of both (N = 5).

History was useful in implicating a genus of insect for non-ant Hymenoptera in 46% of cases. Expertise in insect identification was deemed appropriate in identifying the culprit insect, with four beekeepers identifying honeybees, and two patients that were themselves entomologists (one identifying Polistes, another Vespula). Three of the four beekeepers were only tested for honeybee allergy. The fourth, a patient with mastocytosis, also had anaphylaxis after fire ant stings and was tested and desensitized to both honeybee and fire ant extracts.

Table 1 Elements Used to Implicate the Genus of Insect Causing Anaphylaxis for 52 Patients Undergoing Rush Immunotherapy in New Orleans, Louisiana

Genus Implicated	Element Suggesting Taxon	Patients with Element	% Sensitized to Genus
Solenopsis	Sterile pustule	5	100%
	Witnessed ant stings	13	100%
	Witnessed ant stings +pustule	5	100%
	Stings to lower extremity in young children (unable to provide history)	3	100%
	Specimen or photo provided	0	
Dolichovespula	Paper mâché globe as nest	0	
	Specimen or photo provided	0	
Vespula	Insects swarming from the ground	0	
	Specimen or photo provided	0	
	Patient entomologist	1	100%
Polistes	Open comb umbrella-shaped nest	3	100%
	Specimen or photo provided	3	100%
	Patient entomologist	1	100%
Apis	Patient beekeeper	4	100%
	Specimen or photo provided	0	
None		14	100%

For non-experts, patient descriptions or specimens and/or photos provided useful clues for identifying the insect involved. Polistes was implicated based on patient description of an open-comb, umbrella-shaped nest with three patients. An additional three patients produced a specimen or photograph of the stinging insect identified by our entomologist as Polistes. In these cases, allergy testing confirmed sensitization to the genus of insect implicated.

In cases of Polistes involvement, additional testing revealed sensitization to Dolichovespula and Vespula, potentially due to cross-sensitization or because of a unique sensitization to these species. Using joint decision making, three decided to undergo additional desensitization using a mixed vespid extract.

The initial round of allergy testing performed to verify sensitization to venom (prior to venom immunotherapy) was carried out using serum testing (ImmunoCAP) for 50 out of the 52 patients, consistent with the standard practice among allergists in our local area. This approach, however, contrasts with the practices observed in other regions where skin testing is often done first. Notably, both patients who initially underwent skin testing were specifically assessed for fire ant sensitization only. Additionally, two patients who had initially undergone serum testing with negative results subsequently underwent skin testing, which was positive for fire ant sensitization.

Patient history (or provision of a specimen or photograph) was useful for identifying the insect causing venom-induced anaphylaxis in 73% of our patients. This was disproportionately true for fire ants, where history was useful in 100% of cases versus 46% of cases of other Hymenoptera. For each of these cases, testing confirmed sensitization to the insect implicated by history. These data reaffirm the recommendations for using elements of the history to identify culprit insects, in contrast to common practice of broader testing due to concern that clinically important sensitization might be missed. When testing was conducted with additional Hymenoptera extracts, none of the patients suspected of having anaphylaxis induced by fire ants elected to undergo desensitization with the additional extracts. Additional testing did expand the number of extracts used for other Hymenoptera in a minority of patients. Because we conducted serum testing as the sole method of determining sensitization for most patients, detection of IgE to more venom extracts may have increased[6] although these additional positives are of uncertain clinical significance.

Even in our hospital system with streamlined procedures to initiate immunotherapy, there was an average of 1-year between initial reaction and protection achieved. Using history to direct selection of immunotherapy extracts and eliminating the need for testing would allow for an ultrarush induction to be completed on the date of anaphylaxis for most of our patients and lead to earlier protection. Immediate initiation of immunotherapy may further increase the safety of this procedure by conducting it within the refractory period following an anaphylactic event.

Commencing with rush immunotherapy on the day of anaphylaxis may help overcome barriers to initiation with immunotherapy, but does not address many of the barriers that remain for long-term adherence with the maintenance phase, for which additional research is needed.[3] This approach may be especially useful for patients identifying ants as the cause of a reaction in areas where fire ants are prevalent. For patients with reactions triggered by other types of Hymenoptera, this strategy would be useful to a much smaller proportion of patients, and would rely on expertise in identification of the insects or their nests by experts.

There is a risk that patients with mast cell disorders, for whom anaphylactic reactions can develop despite lack of IgE, would undergo venom immunotherapy despite lack of sensitization. It is not clear whether use of venom immunotherapy in patients with non-IgE mediated reactions would be helpful, harmful, or neither.

While our study provides insights into the reliance on patient history for identifying the causative insect in venom-induced anaphylaxis cases, we acknowledge the need for a nuanced understanding of the generalizability of our findings, particularly in different geographical contexts, especially given the species composition variations of social Hymenoptera in New Orleans compared to other regions in the US.[7] Additional research is needed to determine whether the variables useful for implicating Hymenoptera as triggers for anaphylaxis in the New Orleans area can be extended to other locations. The correct identification of the causative agent in venom allergy is crucial for the success of immunotherapy. Failing to detect and desensitize a clinically-relevant sensitization would fail to protect patients at risk for venom-induced anaphylaxis. Our chart review identified that 29% of patients had and tolerated a field sting to their identified insect without anaphylaxis after induction of ultrarush with no reactions among patients with restricted venom immunotherapy. In order to draw a definitive conclusion about efficacy, further dedicated research is warranted to assess the occurrence of venom anaphylaxis after immunotherapy in real-world scenarios (ie, sting challenge, field stings) when history-directed

testing and extract selection is used. Addressing these aspects will contribute to further refining diagnostic strategies and improving patient outcomes in the management of venom-induced anaphylaxis.

Abbreviations

VIT, venom immunotherapy; WBE, whole body extracts; EMR, electronic medical record; CPT, current procedural terminology; US, United States.

IRB Approval

Granted prior to conducting the study.

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Disclosure

The authors report no conflicts of interest in this work.

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