
Frequency of imported fire ant stings in patients receiving immunotherapy

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Background: Imported fire ant (IFA) stings are an important cause of stinging insect hypersensitivity in endemic areas. IFA stings are difficult to avoid, and many studies have shown high field sting rates. No studies report the natural IFA sting rate that patients experience while receiving IFA immunotherapy.

Objective: To determine the frequency of IFA stings in patients receiving IFA immunotherapy compared with an aeroallergen immunotherapy control group.

Methods: Patients were surveyed by telephone to characterize the frequency of stings, reactions, and attitudes toward IFA avoidance.

Results: A total of 23 of 28 patients reported IFA stings during their IFA immunotherapy compared with 16 of 28 patients during their aeroallergen immunotherapy. More of the IFA immunotherapy-treated patients were stung than the aeroallergen immunotherapy patients, which is inconsistent with our hypothesis ($\chi^2 = 4.139$, $P < .042$). The annualized sting rates between the IFA immunotherapy and aeroallergen immunotherapy groups were similar (1.82 vs 1.72 stings per year, $P < .55$). The IFA immunotherapy patients were more likely to report any kind of reaction ($\chi^2 = 9.124$, $P < .003$) compared with the control group. Most patients reported feeling careful to avoid stings.

Conclusions: Patients with IFA hypersensitivity treated with IFA immunotherapy do not experience a decreased frequency of stings resulting from attention to sting avoidance. IFA stings are frequent and difficult to avoid. Rush IFA immunotherapy is a good option for many patients to achieve protection quickly.

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INTRODUCTION

Imported fire ant (IFA) stings are a frequent cause of stinging insect hypersensitivity in endemic areas. Originally imported through the port of Mobile, Alabama, during the early 20th century, the major clinically relevant IFA species, *Solenopsis invicta*, has since spread throughout much of the southern United States. IFA stings are frequent in infested areas, and patients who are appropriately referred for anaphylaxis caused by IFA stings are often treated with IFA whole-body extract immunotherapy. Reactions to IFA stings can be severe or deadly. A survey of 29,300 physicians performed in 1989 found reports of 84 fatal IFA reactions.¹ IFAs attack both young and elderly people both indoors and outdoors.^{2,3} The overall topic of IFA hypersensitivity was recently extensively reviewed.⁴

The focus of our study was on the frequency of IFA stings while patients are actively receiving immunotherapy. Various sting attack rates have been reported in the literature in different populations. A telephone survey performed in 1973 in Metairie, Louisiana, showed that 226 of 777 respondents

(29%) reported IFA stings during a 3-month period.⁵ Another telephone survey performed during the calendar year 1976 in Georgia included both rural and urban patients.⁶ This survey found a similar frequency of sting attacks, with 95 of 310 individuals (31%) experiencing a total of 213 sting attacks. Stafford et al⁷ proposed an annual sting attack rate of 30% as a conservative estimate, and deShazo et al⁸ proposed an annual sting attack rate of 30% to 60% in urban areas in their respective reviews.

Tracy and colleagues⁹ studied 107 military medical students who came from throughout the United States to attend a 3-week training course in San Antonio, Texas. Surprisingly, 55 (51%) of these students reported IFA stings during their 3-week stay in San Antonio, despite a curriculum composed mainly of classroom instruction. A retrospective survey of patients with IFA hypersensitivity who previously received IFA immunotherapy (patients who never received immunotherapy or who were currently receiving immunotherapy were excluded) found that nearly all patients experienced IFA stings in the years after receiving immunotherapy (32 of 34 patients; mean time since immunotherapy, 7 years).¹⁰

Freeman¹¹ demonstrated that reactions to IFA accounted for 42% of visits to a dedicated venom clinic in an IFA endemic area and that IFA immunotherapy represented 59% of total new venom immunotherapy prescriptions. Partridge et al¹² used anonymous serum samples in an IFA endemic area and found a high prevalence of IFA sensitization, as evaluated by IFA venom specific IgE and IgG. They also applied a survey to a population of 1- to 18-year-old children

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and found that 40% had been stung in the prior month. The unifying theme of these studies is that IFA stings are frequent in endemic areas and difficult to avoid.

What has not yet been studied is the frequency of IFA stings while patients are actively receiving immunotherapy. Patients receiving IFA immunotherapy have experienced serious, sometimes life-threatening reactions to IFA stings and therefore may be more vigilant in sting avoidance. Our hypothesis was that the frequency of IFA stings in patients receiving IFA immunotherapy is less than the frequency in a control group of patients receiving only aeroallergen immunotherapy. Secondary objectives were to determine the occurrence of IFA reactions, the characteristics of those reactions (as local or systemic), the estimated number of occasions of IFA stings, the number of individual IFAs per occasion, and patients' attitudes toward sting avoidance.

METHODS

The study design was an observational, nonconcurrent comparison of treatment groups using a telephone survey. The study was approved by the Wilford Hall institutional review board, and patients who wished to participate gave verbal consent. Inclusion criteria were patients currently receiving IFA immunotherapy (or aeroallergen immunotherapy for the control patients) and who wished to participate. Patients were identified through an electronic immunotherapy administration system. The goal was to survey as many active IFA immunotherapy patients as could be contacted. The aeroallergen control group was matched for age and sex. Parents were questioned for pediatric patients younger than 18 years. Patients were excluded if they did not wish to complete the survey or if they were not actively receiving immunotherapy. If any anaphylactic episodes were discovered that had not already been addressed, then appropriate follow-up was arranged. The questions asked during the telephone survey are given in Table 1. The χ^2 test of proportions was performed using SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Twenty-eight IFA immunotherapy patients and 28 aeroallergen immunotherapy patients were surveyed for a total of 56 study participants. No significant differences were found between the groups in sex, age, or duration of immunotherapy. Patient characteristics are given in Table 2. The goal was to survey all active IFA immunotherapy patients, so some patients had only recently begun immunotherapy.

Table 3 gives the number of patients who reported IFA stings during immunotherapy for both the IFA and aeroallergen groups. More of the IFA immunotherapy patients reported stings than the aeroallergen patients (23 vs 16, $\chi^2 = 4.139$, $P < .042$) during their immunotherapy.

Annualized sting rates were calculated for each treatment group by using the total number of sting occasions as the

Table 1. Questions Asked During Telephone Survey

1. Have you been stung by fire ants since you started immunotherapy (allergy shots)?
2. If so, on how many occasions have you been stung?
3. Did you have a reaction to your stings?
4. If so, what kind of reaction? (Patients described their symptoms and the reaction was classified as local if symptoms were contiguous with the sting site with no systemic symptoms, or systemic if any systemic symptoms occurred, ie, cutaneous symptoms not at sting site, respiratory, gastrointestinal, or other systemic symptoms.)
5. (In case of systemic symptoms): Has this been evaluated by an allergist?
6. (For patients treated with IFA immunotherapy): Was the reaction better, worse, or the same as reactions you had before starting allergy shots for fire ants?
7. (For patients treated with IFA immunotherapy): Do you feel more careful to avoid fire ant stings since you started fire ant immunotherapy?
8. (For aeroallergen immunotherapy patients, not treated with IFA immunotherapy): If you were stung by fire ants, do you feel more careful to avoid fire ant stings?

Abbreviation: IFA, imported fire ant.

Table 2. Patient Characteristics

Characteristics	IFA immunotherapy patients (n = 28)	Aeroallergen immunotherapy patients (n = 28)
M/F, No.	10/18	10/18
Mean (range) age, y	43.6 (6–72)	42.1 (7–72)
No. of patients ≤ 21 years old	7	7
Mean (range) duration of immunotherapy, y	4.24 (0.08–25)	4.31 (0.25–22)

Abbreviation: IFA, imported fire ant.

numerator and the total duration of immunotherapy as the denominator and are presented in Table 3. The total number of sting occasions reported by each group was remarkably similar, and no statistically significant difference was found between the sting rates (1.82 vs 1.72 sting occasions per year for the IFA and aeroallergen immunotherapy groups, respectively; $P < .55$). Although the total number of patients experiencing stings in the IFA immunotherapy group was higher, no significant difference was found in IFA sting rates over time between the IFA immunotherapy and aeroallergen immunotherapy groups. These findings are inconsistent with our hypothesis that IFA immunotherapy patients are stung less frequently than non-IFA immunotherapy patients while receiving immunotherapy.

As for the reactions reported after IFA stings, 14 of 23 IFA immunotherapy patients reported reactions, and 2 of 16 aeroallergen immunotherapy patients reported reactions. No patients reported more than 1 reaction. The 2 reactions in the aeroallergen immunotherapy group were local reactions. Of

Table 3. Annual IFA Sting Rates and Reactions to IFA Stings^a

Variable	IFA immuno-therapy	Aeroallergen immuno-therapy
No. (%) of patients stung	23 (82)	16 (57)
No. (%) of patients not stung	5 (18)	12 (43)
Total No. of patients	28	28
No. of sting occasions	216	208
Total duration of immunotherapy, y	118.8	120.7
No. of sting occasions per year	1.82	1.72
No. of local reactions	10	2
No. of systemic reactions	4	0
Total No. of reactions ^b	14	2
No. of patients with no reactions	9	14

Abbreviation: IFA, imported fire ant.

^a For number of IFA immunotherapy patients stung vs aeroallergen immunotherapy patients stung, $\chi^2 = 4.139$, $P < .042$. For annualized sting rates between the IFA immunotherapy and aeroallergen immunotherapy groups, $P < .55$. For the total number of reactions between the 2 groups, $\chi^2 = 9.124$, $P < .003$.

^b No patient who was stung reported more than 1 reaction.

the 14 reactions occurring in the IFA immunotherapy group, 10 reactions were local and 4 were systemic. Three of the systemic reactions occurred in patients who were not receiving the maintenance dose of immunotherapy, either because they had not yet reached maintenance or because they were reduced because of time since last injection and were building up again. Two of these patients reported that their reactions were less severe than before starting immunotherapy; 1 patient reported that the reaction's severity was the same. They have since followed up with their assigned allergists. One systemic reaction occurred in an 11-year-old boy who was receiving his maintenance dose. His symptoms were mild and less severe than the reaction he had before starting IFA immunotherapy. Subsequently, his maintenance dose was increased from 0.5 to 1.0 mL of the red 1:1 vol/vol vial (1:100 wt/vol in the prior nomenclature). The red 1:1 vol/vol vial contains 1 mL of IFA whole-body extract and 9 mL of diluent. After achieving the higher maintenance dose, he experienced a field sting without any systemic symptoms. IFA immunotherapy patients were more likely to report any kind of reaction ($\chi^2 = 9.124$, $P < .003$). The reaction data are summarized in Table 3.

Despite stings occurring in most patients surveyed in the study, both groups reported a high degree of attention to sting avoidance. Twenty-two of 28 IFA immunotherapy patients (78.6%) reported feeling more careful to avoid IFA stings after starting IFA immunotherapy (95% confidence interval, 63.4%–93.8%), and 14 of 16 aeroallergen immunotherapy patients (87.5%) reported feeling more careful to avoid IFA stings after having had IFA stings (95% confidence interval, 71.3%–100%).

The IFA immunotherapy patients reported a range of 1 to 10 IFAs per sting occasion for a mean of 3.9 per occasion. The aeroallergen immunotherapy patients reported a range of

1 to 95 IFAs per sting occasion for a mean of 6.9 per occasion. The number of estimated IFAs per sting occasion is interesting, but the quality of this data is limited because of patients' difficulty in remembering the exact number of ants.

DISCUSSION

In this population, patients with IFA hypersensitivity treated with IFA immunotherapy do not experience a decreased frequency of IFA stings that may result from increased vigilance and attention to sting avoidance. A greater number of patients receiving IFA immunotherapy reported IFA stings during immunotherapy compared with a control group receiving only aeroallergen immunotherapy, despite most patients professing care in avoidance of stings. No significant difference was found in the annualized sting frequency between groups, which is inconsistent with our hypothesis that the IFA immunotherapy patients are stung less frequently because of greater attention to sting avoidance.

This study provides further evidence that IFA stings are extremely difficult to avoid in endemic areas, even in patients who are actively receiving immunotherapy for a potentially deadly condition. The annualized sting rates we report (1.82 and 1.72 stings per year for IFA immunotherapy and aeroallergen immunotherapy patients, respectively) are similar to the rate reported by Adams and Lofgren⁶ during calendar year 1976 in Georgia (213 total sting attacks divided by 95 individuals reporting stings equals 2.24 stings per individual in 1 year).

There are some parallels to our findings in the flying Hymenoptera literature. Stone and colleagues¹³ surveyed 29 flying Hymenoptera-sensitive patients concerning the prior 2 years while they were receiving venom immunotherapy and compared these patients to 28 control patients.¹³ They found that venom immunotherapy-treated patients were stung more frequently than the control patients (2.03 vs 0.214 mean stings in 2 years per patient, respectively), despite venom immunotherapy patients showing greater knowledge of sting avoidance. Twenty-three of the same patients were resurveyed 3 years after the first survey either during or after their courses of immunotherapy.¹⁴ In this study, only 30% of the patients reported stings compared with 87% from the first study. The authors speculate that venom-allergic patients have some sort of intrinsic factor that attracts insect stings and then fades during venom immunotherapy. Whether IFA-allergic patients have an intrinsic quality that attracts stings is unknown. An individual's behavior probably contributes to an increased risk of stings in IFA-allergic patients (eg, greater time spent outdoors, walking barefoot).

Patients with IFA hypersensitivity are effectively treated with whole-body extract¹⁵ and are often selected for 1- or 2-day rush protocols^{16,17} to gain protection faster than conventional build-up schedules because of the difficulty in avoiding stings in endemic areas. These trials demonstrated the efficacy of IFA whole-body extract for IFA hypersensitivity. Immunotherapy is usually given for a period of 3 to 5

years but can be given lifelong in case of a life-threatening initial reaction.¹⁸ The natural history of IFA hypersensitivity has not been fully described.

The principal finding of our study, that IFA stings are frequent even while patients are receiving IFA immunotherapy, supports the role of rush IFA immunotherapy for certain patients to achieve rapid protection. Conventional build-up schedules usually take 4 to 6 months and leave patients exposed during that period to a higher risk of anaphylactic events to IFA stings. For example, 3 of our patients experienced systemic reactions to field stings while they were not receiving the maintenance dose of IFA immunotherapy. One of these 3 patients initiated IFA immunotherapy with a modified 1-day rush schedule, stopping at 0.05 mL of the red 1:1 vol/vol vial, with a plan to build up under a conventional schedule to a maintenance dose of 0.5 mL. She experienced a reaction to a field sting 15 days after receiving a build-up injection (0.07 mL of the red 1:1 vol/vol vial). Rush IFA immunotherapy schedules are a useful option for many patients and can shorten the time required to achieve the maintenance dose. The observation that 1 patient unfortunately experienced a reaction to a field sting after starting rush IFA immunotherapy (but before achieving maintenance) highlights the potential benefit of achieving protection sooner rather than later. Also, physicians can use the data presented herein concerning the frequency of IFA stings for an individualized conversation concerning the duration of immunotherapy with patients whose initial reaction was life-threatening.

Our study is limited because of its observational nature and relatively small sample size. Also, the number of sting occasions and number of ants per occasion are limited by recall bias. No information was collected concerning the exact circumstances surrounding the sting event or specific protective measures. However, given the high frequency of stings seen in other studies in endemic areas, it is uncertain how effective protective measures are in preventing IFA stings in a population. Furthermore, the intent of this study was to evaluate the overall frequency of stings in a high-risk population, so the exact sting frequency in a given individual will vary. There may be individual patients who are successful with IFA sting avoidance.

Future, preferably prospective, studies that survey the exact circumstances surrounding sting events and expanded demographic characteristics (such as occupation and hobbies) will further define the risk of sting attacks in endemic areas in patients currently receiving IFA immunotherapy. Also, surveying methods that patients currently use to avoid stings (such as IFA identification, avoidance of mounds, wearing proper attire when outdoors, and use of insecticides to suppress IFA proliferation of urban lawns) can help identify which techniques may be most effective and can better focus efforts at patient education.

The present study was strengthened by comparison of IFA patients to a control group of aeroallergen patients, and recall bias was minimized by not asking patients to

recall stings per a specific unit of time. Rather, they were simply asked to remember stings that have occurred during immunotherapy. This study is the first report of IFA sting frequency while patients are actively receiving immunotherapy.

In conclusion, this initial study shows that patients with IFA hypersensitivity treated with IFA immunotherapy do not experience a decreased frequency of IFA stings compared with patients without IFA hypersensitivity receiving aeroallergen immunotherapy. Despite an effort to avoid stings, IFA stings are common among patients receiving IFA immunotherapy at our center. Future studies evaluating specific sting avoidance measures can help determine whether this natural sting attack frequency can be reduced with expanded efforts at patient education.

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