Anaphylaxis Reaction to Samsum Ant (Pachycondyla Sennaarensis): A Case Series Study

Abstract

Purpose: Anaphylaxis is a life-threatening hypersensitivity reaction. The present study aimed to investigate the cases of anaphylaxis to ant stings in Iran to determine the characteristics of patients, geographical distribution and the type of ants that cause anaphylaxis. **Patients and Methods:** Patients with a history of anaphylaxis to ant sting underwent skin allergy test with extracted substance from Solenopsis Invicta. Samples of ants were collected from the sites where each patient was bitten and their species were identified by a medical entomologist. **Results:** Nineteen patients (mean age: 26.2 years; range: 4-48 years) were included in the study. Most patients (89.5 percent) were female. The lower limb was the most common site of the sting and most stings had occurred in the morning (31.6 %) and evening (31.6%). Skin manifestations were the most common clinical symptoms (94.7%). Most cases of stings were observed in the Hormozgan province (89.5%) located in southern Iran. Sixteen patients had positive skin prick test for ant venom. All collected ants that caused anaphylaxis belonged to the Pachycondyla Sennaarensis species. **Conclusion:** Ant sting anaphylaxis is not uncommon in Iran, especially in its southern regions. All cases of anaphylaxis in this study were due to samsum ant sting (Pachycondyla Sennaarensis), which is a species similar to the fire ant (Solenopsis Invicta). Allergy skin testing with fire ant extract was positive and helpful in identifying samsum ant allergy in all cases.

Keywords: Anaphylaxis, Ant Venoms, Insects Allergy

Impact Statement: This study is the first case series report from anaphylaxis to ant sting in Iran and all cases of anaphylaxis in this study were due to samsum ant sting.

Introduction:

Anaphylaxis is an acute systemic hypersensitivity reaction caused by the release of various mediators from mast cells and basophils and can be induced by various triggers, including foods, drugs, and stinging insects (1-3). Stinging insects of the Hymenoptera order can cause anaphylaxis. Systemic allergic reactions to insects stings are reported by up to 3% of adults and about 1% of children have a medical history of severe reactions to insect sting (4). In a cross-sectional study of Bemanian et al., the frequency of anaphylactic reaction in adults and children was 169 and 46 cases per 100,000, respectively (5). There are three families of clinically significant Hymenoptera: the bees (honeybees, bumblebees), vespids (yellow jackets, hornets, wasps), and stinging ants. There are several species of ants that their stings can lead to anaphylaxis, including Formicidae such as fire ants (Solenopsis Invicta), Myrmecia spp, Pogonomyrmex spp, and Pachycondyla spp (6). Fire ants are responsible for most allergic reactions to ant stings in the United States (7). Jack jumper (Myrmecia pilosula) in Australia, Pogonomyrmex spp in Canada and Pachycondyla spp in Asia and the Middle East are the most common causes of ant stings hypersensitivity (8-10). In Africa and the Middle East, reported cases of ant sting anaphylaxis are almost always caused by Pachycondyla (Brachyponera) Sennaarensis (10). There have been no reports of anaphylaxis to ant in Iran until now. In this study, we present the first report of anaphylaxis to ant in Iran over 10 years as a case series.

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MATERIALS AND METHODS

This study was conducted at the Allergy Research Center of Rasool-E-Akram Hospital in Tehran, Iran. The study was conducted in full accordance with the principles outlined in the Helsinki Declaration of 1975. The study protocol was reviewed and approved by the Human Research Ethics Committee of Iran University of Medical Sciences (Approved Number: IR.IUMS.FMD.REC 1394.2272). All participants signed an informed consent form after being informed about the study protocol.

According to scattered reports of anaphylaxis to ant stings in Iran, after contacting Iranian allergists, they were asked to refer all cases of ant anaphylaxis from 2004 to 2014 to the Allergy Research Center of Rasool-E-Akram Hospital in Tehran and a private allergy clinic in Yazd. All patients who had a history of generalized systemic allergic reaction to ant and their history were compatible with clinical criteria for the diagnosis of anaphylaxis were included (11). Subjects were excluded from the study if investigation based on the patient's history indicated that no systemic reaction had occurred or that the ant sting was not the cause of the reaction. At study enrollment, patients' demographic and clinical characteristics, including their age, sex, time of the incident, geographical location, clinical manifestations of the reaction, any history of hypersensitivity to ant bites, medical history, and history of drug or alcohol use before the reactions were recorded. In addition, the records of patients at emergency department, where patients were admitted in case of hypersensitivity reactions, were reviewed and the data were integrated. The severity of the anaphylactic reaction for each individual was rated as mild, moderate, or severe according to the criteria published by Brown (12). This rating is based on the clinical manifestations of the anaphylactic reaction and the organs involved in the anaphylaxis. We asked a family member or friend of the participants who had no history of ant allergy to collect four samples of ants from each place where the patient reacted. The ants' specimens were identified by a medical entomologist regarding their unique entomologic phenotype. In addition, participants were asked to identify the ant responsible for their reaction based on the appearances of the ants.

All subjects underwent skin prick test with extracted substance from Solenopsis Invicta (commercial solutions of Holister-Stier Allergy Company, Chicago, USA). The tests were performed by an allergist according to the manufacturer's recommended protocol at the hospital. Patients with negative response in skin prick test underwent intradermal skin allergy test with ten times diluted extract. All tests were done with histamine chloride 10 mg/ml as positive and sodium chloride 0.9% as negative controls. The test response was read after 15 minutes. A wheal diameter caused by tested allergens more than 3 millimeter compared to the negative control was considered as a positive response and sensitization to that allergen.

Statistical analysis

Statistical analysis was performed using Stata statistical software (Stata 13, Stata Corp, Texas, USA). Descriptive data were expressed as mean (standard deviation) or median (range) for continuous variables and number (percent) for categorical variables, respectively. Data regarding features of sting, clinical manifestation, medical history and severity grading of anaphylaxis were

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further summarized in respective tables.

Results:

Nineteen participants (mean age: 26.2 years; range: 4-48 years) met the inclusion criteria. The majority of subjects (17 out of 19) were female. Data related to occurred reactions after ant sting, such as reaction characteristics, geographic locations, and anatomical locations, are presented in Table I. Most stings had occurred in the morning (31.6 %) and evening (31.6%) (Table I). Most cases of stings were observed in Hormozgan province located in the south of Iran (89.5%) and the capital of Hormozgan province in Bandar Abbas (47.4%) (Figure 1 and 2). The lower limb was the most common site to be bitten (Table I). Each patient had an average history of 4.2 previous systemic reactions due to ant sting (range 2-10 times). Ant sting in most cases led to a systemic reaction (94.7%), and local reaction occurred only in 5.3% of patients. According to patients' medical records, 78.9% had a history of at least one atopic disease. Allergic rhinitis (73.3%) and asthma (15.8%) were the most common allergic diseases among the participants. In 31.6% of cases, subjects had a history of underlying disease, the most common of which was cancer. Family history of patients showed that 52.6% of subjects had a family history of allergic disorders. Among family members, the prevalence of allergies was higher in mothers (21.1%) and asthma was the most common allergic disease (21.1%). A summary of the participants' medical history is provided in Table I.

The mean time interval between stings to the first clinical manifestation was 3.7 minutes (range 1-10 minutes). Information on the clinical manifestations after sting and its management are presented in Table II. According to the records of patients admitted to the emergency departments, skin manifestations were the most common clinical symptoms, which occurred in 94.7% of patients (Table II). Pruritus, flushing, and dyspnea occurred in 89.5%, 73.3%, and 73.7% of subjects, respectively. None of the participants had cyanosis, abdominal cramp, bronchospasm, or incontinence (Figure 3).

After the sting incident, Patients were evaluated in terms of actions after the sting. Most cases (89.5%) referred to the emergency department and two patients had taken oral antihistamines themselves and did not go to the emergency department. At the time of the ant sting, only 21.2% of patients had epinephrine, but none of them used it at the time of the attack. Of the 15 patients referred to the emergency department, 88.2% responded well to the first dose of epinephrine and 11.8% required repeated epinephrine (Table II). None of the patients needed cardiopulmonary resuscitation. The average length of stay in the emergency room was 2 hours (range 1 to 5 hours). Out of 15 patients referred to the emergency department, three patients (17.6%) needed to be hospitalized. After discharge, EpiPen (self-injecting epinephrine) was prescript to only four patients and no action plan for anaphylaxis was given to any patient.

According to Brown's model for classifying the severity of anaphylactic reactions (12), moderate reactions were the most common anaphylactic reactions (57.9%). The results of grading the severity of anaphylactic reaction in participants are presented in Table II.

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Participants' allergy to ant venom was confirmed by skin allergy tests. Initially, all patients underwent skin prick test (SPT). The SPT results showed that 16 out of 19 patients have positive SPT for ant venom. The other three patients were then tested by intradermal test and we found that they were also allergic to ant venom. Two patients showed a systemic reaction during skin tests and were treated immediately.

A medical entomologist evaluated the collected ant samples to determine the species of ants that caused the allergic reactions. He confirmed that all ant samples belonged to Pachycondyla Sennaarensis species (Figure 4).

All patients were asked to receive immunotherapy and 42.1% accepted the proposed treatment. Patients stated that the most common reason for not participating in immunotherapy was the high cost of treatment (Table II). Venom immunotherapy was performed with the GREER® (Allergenic extracts – Ant Fire, Solenopsis Invicta; Lenoir, United States of America). Of the eight patients who underwent immunotherapy, 50% had adverse reactions to immunotherapy. The most common complication was a local reaction at the injection site. Of the eight patients treated with immunotherapy, six were re-sting by ants, and only one developed anaphylaxis (Table II)

Discussion:

The prevalence of anaphylaxis in the US population is estimated at 1.6 – 5.1% (13). Anaphylaxis to insect stings is responsible for 20-30% of all anaphylaxis cases referred to emergency services (13, 14). It is estimated that about 0.4 to 0.8% of children and 2 to 3% of adults experience a systemic reaction to insect stings during their lifetime (15, 16). Anaphylaxis following insect stings is a major challenge for allergists. The mortality rate from anaphylaxis due to insects sting is reported to be approximately 0.1 cases per million population (17).

Some ants are in the group of stinging insects. However, in a small number of ants, their stings cause allergic reactions (18). Pachycondyla Sennaarensis (PS) is an ant species widely distributed throughout sub-Saharan Africa and the Middle East (19, 20). In some countries around the Persian Gulf, there have been reports of anaphylaxis due to the sting of PS (21, 22). In a case report from Saudi Arabia in 2009 by AlAnazi et al., they reported four patients with anaphylaxis due to PS (22). They described that PS ants, like fire ants, inject their venom with a sting and do not bite. In Iran, the presence of PS was first reported in 2004 by Akbarzadeh et al. in Sistan and Baluchestan (a province in southeastern Iran). They described the ant's morphology with a punctuated head and chest, a mandibular triangle, and seven teeth (23). In a study conducted by Pakpa et al. In Iran, they found that PS was more prevalent in Iran, especially in the south (24). Most reported cases of ant stings in Iran were in Hormozgan province in southern Iran and most of them were from Bandar Abbas city in this province. By comparing the distribution of PS ants in Iran as mentioned and the distribution map of ant bites in this study (Figure 1 and 2), we understand that they are in the same areas. Khoobdel and his colleagues

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claim that shipping to southern countries around the Persian Gulf may be the cause of the PS entering Iran (25).

In a study by Nikbakht et al. in 2009, they claimed that there was no report of anaphylaxis following PS stings from Iran until that time. Based on their research in the biology and chemical diversity of PS abdominal glands, they explained the lack of anaphylaxis with low protein content in the abdominal glands of PS in Iran (26). Here, we report 19 cases of anaphylaxis following PS sting, which is the largest report on this issue from the Middle East. Most cases of anaphylaxis to the PS sting lived in southern Iran.

The mean age of patients in our study was 26.2 years and most cases were female (17 out of 19 years). The mean age of patients in other studies of anaphylaxis to insect stings in Australia and Spain were 46 and 40 years, respectively (8, 27). Comparing the mean age of the population of Iran and other countries in which the above studies have been performed (Iran = 28.3, Australia = 38.3 and Spain = 41.6) shows that the population of Iran is younger than Australia and Spain. It may be explained why patients' mean age in our study was lower than other studies. In most studies of anaphylaxis to insect stings, there was no significant difference in prevalence between men and women (12, 28-30). In our study, the prevalence of anaphylaxis to insect bites was significantly higher in women. It is difficult to explain the reason for this observation due to the small number of cases.

In the present study, most stings occurred in the morning and evening. In a survey by Khoobdel et al. on the biological behavior of ants in the tropics and subtropics, they explained that ants leave their nests shortly before sunrise and work for several hours as the earth warms. They return to their nest, and if they are far away, they hide in the hole of the earth and resume their activity in the evening (25). This behavior of the ants may explain why most of the stings occurred in the morning and evening.

In current study, the lower limb was the most common anatomical site of the sting. In the study of Khoobdel et al. on ant bites in Abu-Musa Island, in the south of Iran, the lower limb was also the most stinging site (50.7%) (25). It is probably because the lower limbs are the most accessible part of the body for ants.

Skin manifestations were the most common clinical manifestations in our study, followed by respiratory, cardiovascular, neurological, and gastrointestinal manifestations, respectively. In a survey conducted by Jirapongsananuruk et al. in Thailand on the characteristics of patients admitted with anaphylaxis, the most common manifestations were cutaneous (86%), respiratory (80%), Cardiovascular (52%) and gastrointestinal (36%), respectively (29). In another study by Brown et al. on 1149 patients with anaphylaxis in Australia, pruritus (73%), erythema (48%), angioedema (32%) and dyspnea (29%) were the most common symptoms (12). In our study, pruritus, dyspnea and flushing were the most common symptoms. The order of common manifestations in our study seems to be almost the same as in Brown's and Jirapongsananuruk's studies. In addition, three patients (17%) of all our subjects required hospitalization, which is in line with the result of Jirapongsananuruk's study, where 12% of patients with anaphylaxis were hospitalized (29).

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On average, the patients had a history of four-time stings leading to anaphylaxis in their history. A study by Webb et al. on anaphylactic patients showed that more than half of the patients experienced more than three episodes of anaphylaxis (30).

In our study, 78.9% of patients had a history of atopic disorder. Allergic rhinitis, asthma and urticaria were the most common diseases in 73.7%, 15.8% and 10.5%, respectively. In the study of Jirapongsananuruk et al. in anaphylactic patients, 52% of cases had a history of atopy and the most common atopic diseases were asthma (26%), allergic rhinitis (20%) and drug allergies (16%) (23). In another study by Web et al., anaphylaxis was more common in atopic patients, in which 54% of cases with exercise-induced anaphylaxis and 50% of patients with food-induced anaphylaxis had a history of atopic disorders (30).

In a study by González-Pérez et al., the incidence of anaphylaxis was higher in patients with asthma than in patients without asthma, and this rate was higher in severe asthma (31). In a patient with asthma, special attention should be paid to controlling respiratory manifestations. Several studies have shown that inadequate treatment of asthma is a significant risk factor for severe anaphylaxis (32, 33).

Alcohol and drug use before anaphylaxis may affect the severity of attacks (34). In our study, no one had consumed alcohol, and 15.8% of them had taken drugs such as aspirin, ibuprofen, and cetirizine. In the study of Wölbing et al. regarding the effect of cofactors on anaphylaxis, they found that the use of alcohol and drugs (such as NSAIDs) can cause a more severe reaction with a small amount of allergen and reduce the interval between exposure to allergens and anaphylaxis (35).

Regarding the underlying disease, 31.6% of the evaluated patients had underlying disease, including cancer (10.5%) (breast and uterine cancer), cardiovascular diseases (5.3%), thalassemia (5.3%), Favism (5.3%) and Diabetes (5.3%) In the Jirapongsananuruk's study of anaphylactic patients, 31% of them had an underlying disease, which the most common disease were: cancer (11%), cardiovascular diseases (7%) and neuromuscular diseases (6%) (29). Cancer and cardiovascular disease appear to be the most common underlying diseases in patients with anaphylaxis.

We asked patients about the history of ant stings without anaphylaxis, and only 5.3% reported having a history of ant stings without anaphylaxis. Given that in IgE-mediated systemic reactions to Hymenoptera sting, the previous sting is necessary for sensitization to venom proteins, and systemic reactions occur only with repeated stings after previous sensitization. We suspect that the reason why most patients, contrary to expectations, did not report a history of ant sting before anaphylaxis may be that patients had mild and non-systematic reactions to the initial stings and forgot the mild reactions due to its low severity and only recalled severe systemic reactions to ant stings.

About family history of allergic disease in the evaluated patients, 52.6 % of them had a family history of allergic diseases. It was more common in the mother of patients (21.1%) and the most

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common disease was asthma (21.1%). In our cases, allergic rhinitis was the most common atopic disease in their history and asthma was the most common atopic disease in their family. In a study by Sheffer et al. about exercise-induced anaphylaxis, they found that all patients had a family history of allergic rhinitis and 13 % of them had a family history of asthma (36)

Skin allergy tests were performed on all our patients and all of them had positive skin tests. We used Solenopsis Invicta extract instead of Pachycondyla sennaarensis extract in the skin tests as PS extract was unavailable. Although the PS ant sting was responsible for anaphylaxis in all cases in our study, skin tests with Solenopsis Invicta extract were positive in all patients. The similarity between the materials extracted from s.invitca and PS seems to lead to a positive result in skin testing.

Two patients showed anaphylactic manifestations during skin allergy test and were treated immediately. This indicates that although the amount of substance used in the skin allergy test is minimal, it may lead to anaphylaxis and a well-equipped medical team should be present in the test room. In a study on the risk of anaphylaxis during skin allergy test by Licardi et al., they found that the risk of anaphylaxis during skin prick test was less than 0.02% and with intradermal skin test was higher, and in some cases, intradermal skin test could be fatal. Given this risk, they recommended that intradermal testing should not be the first option for assessing allergies (37). The high rate of anaphylaxis in the skin allergy test in our study seems to be due to selected patients, all of whom have a history of ant sting anaphylaxis.

According to the classification system of severity of anaphylactic reactions presented by Brown et al. (12), we found that most anaphylactic reactions in our patients were moderate (57.9%) followed by severe (36.8%) and mild (3.5%). In Brown's study, they analyzed 1149 patients with anaphylaxis. Most of anaphylactic reactions were severe (68%), followed by moderate (42%) and mild (15%). When they focused on patients with anaphylaxis due to insects stings, they found that most reactions were moderate (47%), then mild (35%) and severe (16%). It seems that in patients with anaphylaxis due to insect bites, most patients show a moderate reaction.

It should be noted that in the present study, Iranian allergists were asked to refer patients with a history of ant sting anaphylaxis. It may reduce the actual number of cases of ant sting anaphylaxis due to the probable cases that have not been referred to an allergist. The use of patients' previous history may also affect our data recall biased. Furthermore, another limitation of the present study is that the Samsum ant extract was not available to us for skin testing. Instead, we used fire ant extract. Although all of our cases had a positive skin test to fire ants (probably due to the similarity of the allergens in the extracts), it would be better to use Samsum ant extract for skin testing.

Conclusion:

This report is the first case series of anaphylaxis to ants in Iran and the largest report in this field in the Middle East. The present report shows that ant sting anaphylaxis is not uncommon in these areas. Although fire ants (Solenopsis Invicta) are the most common cause of ant stings in Europe and the United States, all cases of anaphylaxis in this study were due to the sting of samsum ant (Pachycondyla sennaarensis), a species similar to the fire ant, that is found in the south of Iran,

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the Middle East and North Africa. Allergy skin testing with fire ant extract was positive and helpful in detecting samsum ant allergies. In cases where smsum ant extract is not available, fire ant extract may be a good alternative to Samsam ant skin test.

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Conflict of Interest: The authors declare absence of economic or other types of conflicts of interest regarding the article presented.

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