Anaphylactic Reaction to a Bee's Sting in Rural Areas of Gorgan City: The first Epidemiological Study of Anaphylaxis due to Hymenoptera in Iran

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Abstract

Objective: To determine the epidemiology of anaphylaxis to a bee's sting in the rural areas of Gorgan city.

Methods: In this cross sectional study, we analyzed some of the epidemiological characteristics of the study participants such as demographic information, bee type, cause of anaphylaxis, time of bee sting, onset of symptoms of anaphylaxis after a bee sting, number of bee stings, symptoms during anaphylaxis, and therapeutic and prophylactic measures.

Results: 201 patients were diagnosed with anaphylaxis caused by a bee sting. Of these, 129 (64%) were male and 72 (36%) were female with an average age of 34.33 (32) and 35.25 (34) years respectively. Anaphylaxis incidents occur in 108 men and 103 women out of 100,000, 169 of which are adults and 46 are children. Anaphylaxis occurred in 105 cases (52.2%) less than five minutes after being stung (very severe attack) and in 94 cases (46.8%) between 5-60 minutes after being stung (rapid attack) (p = 0.45). The patients' organs involved were skin (85.6%), respiratory system (78.6%), cardiovascular system (35.8%), nervous system (17.4%) and gastrointestinal tract (10.9%). Among these stings, 78 (38.8%), 107 (53.2%) and 16 (8%) took place indoors, outdoors and at home respectively (P=0.05). Seven (9.5%) children and sixty seven (39.6%) adults had hypotensive symptoms (P= 0.05). Ninty five percent of cases have been stung less than 10 times, and 80% of those who have experienced more than 10 stings had severe anaphylactic attacks (P = 0.003).

Conclusion: Based on our study, case finding was successful through the rural health network. In order to obtain accurate epidemiological information on the prevalence of anaphylaxis due to bee stings, an anaphylaxis registry and healthcare service packages are recommended. In this integrated model, a service package, including raising awareness and knowledge of people, and treatment for anaphylaxis can be employed.

Keywords: Epidemiological characters; Bee sting, Gorgan; registry

Introduction

Bees are a member of the Hymenoptera family and their sting has been recognized as one of the most important causes of anaphylaxis reactions in humans for thousands of years (1, 2). The first recorded death by a bee sting was due to a Paper Wasp sting and it was related to the Egyptian pharaoh, which was based on a Bee sting in 2000 BC. The common response to this plain sting is usually transient pain, itching and swelling, however it can lead to severe localized reactions or systemic reactions. Five percent of people experience large or prolonged localized swellings at the site of the sting following a bee sting. Hymenoptera is a large group of insects that include three main families; (1) Apidate (honeybee and bumblebees) (2) Vespidae (hornets, wasps and yellow jackets) and (3) Formicidae (fire ants) (3).

The incidence of deadly anaphylactic reactions caused by insect stings, such as bees, is between 0.03 to 0.48 deaths per million each year, accounting for approximately 20% of deadly anaphylactic reactions. Bee sting allergy is observed in 26% of adults, however it can increase to 30-40% in cases who have had a history of bee stings in recent weeks (4). With the advancement and development of allergy science many preventive measures, especially therapeutic ones, have been proposed to improve the condition of patients with anaphylaxis caused by bee stings, the most important of which are diagnostic measures for identifying the bee causing anaphylaxis and performing immunotherapy for said bee venom (5). To implement large and strategic planning and design appropriate diagnostic and therapeutic measures for patients with anaphylactic reactions caused by bee stings, health policymakers require detailed information about the various epidemiological indicators of this reaction at the national level and need to assess physicians, medical staffs, and patients' level of knowledge on this case. , There has been no comprehensive study on the frequency distribution of patients with bee sting-induced anaphylaxis reactions and their symptoms as well as the necessary diagnostic and therapeutic measures at different levels in the Iranian healthcare setting. Golestan province is one of the leading provinces in terms of recording and completing population health data in the country's healthcare network. At present, all health data is being completed in electronic form, collected and recorded online through the E-health software (NAB Program). It seems that conducting an appropriate epidemiological study in this field can provide the grounds in Golestan, as one of the leading provinces, for establishing the basis of a national registration system and data base for patients with anaphylaxis reaction caused by bee stings. Accordingly, the present study was conducted to evaluate the epidemiological determinants of anaphylaxis cases caused by bee stings in Gorgan Province until the end of 2017.

Patients and Method

This cross-sectional epidemiological study was performed on patients residing in rural areas of Gorgan County in 2017, who have a history of anaphylactic reactions to bee stings. Patients' data was collected through house-to-house visits by the iranaian community rural health workers (Behvarz).. To record this information, patients with a history of severe bee sting allergy and those with a history of bee stings were identified in the initial stage via the completion of a questionnaire. In the next stage individuals with a history of possible anaphylaxis were selected.. All identified cases were referred to an allergy and clinical immunology specialist who evaluated the patient's history of anaphylactic reactions and confirmed its cause to be due to a bee's sting.

Among the individuals who met the criteria to be included in the study, those who had non-systemic reactions caused by a bee sting or their anaphylaxis (mild, moderate and severe) allergy caused by a fire ant venom were excluded from the database in the final stage of registration. The census sampling was carried out in this study and all the data registered in the database by the end of the year 2017 was studied. The basic information and clinical records obtained from the database were collected through oral interviews.

Statistical analysis: All data obtained from the database were later analyzed in SPSS ver. 21 and SAS ver. 9.1. Quantitative and categorical qualitative variables were described using mean ± SD and number and percentage. The quantitative variables of this study were compared using t-test or Mann-Whitney U test in case of abnormal distribution. The comparison between qualitative variables was also performed using Chi-square or Fisher's exact tests. Pearson correlation coefficient test and Spearman rank correlation were also applied to investigate the correlation between quantitative variables. Multivariate logistic regression analysis was used to determine the differences in the study indices in patients and in the presence of the patients' baseline, characteristics as confounding factors and the results were expressed as odds ratio (a 95% confidence interval). P-value<0.05 was considered as the statistical significance level.

Results

The data of this study was collected from a database of bee stings in 84 health housesin villages around Gorgan County with a population of 140,000 people (NAB program). A total of 201 patients with bee sting-induced anaphylactic reaction were present in the database throughout the study period. Of these, 129 (64%) were men with an average age of 34.53 ± 18 years and 72 (36%) were women with an average age of 35.25 ± 15.7 years. The frequency distribution of the anaphylaxis was 188 and 103 cases in men and women respectively, with a total of 144 cases per 100,000 population of the total population of men and women covered. The anaphylaxis reaction frequency in adults and children was 169 and 46 cases per 100,000 populations covered, respectively. The frequency of mild, moderate and severe anaphylaxis in this study was 43, 54 and 47 cases per 100,000 population covered, respectively. The highest frequency of anaphylactic reaction was observed in the summer and after spring, with a frequency of 70 and 56 cases per 100,000 populations respectively, and this frequency was reported to be 15 and 1 per cases per 100,000 populations in autumn and winter, respectively. Of the patients whose information was included in the bee sting database, 105 cases (52.2%) experienced anaphylactic shock (a very rapid attack) in less than five minutes after being stung, and in 94 cases (46.8%) anaphylactic attacks occurred

between 5-60 minutes after being stung (rapid attack). In this study, the frequency of anaphylactic reaction was 79 (39.3%), 98 (48.8%), 23 (11.4%) and 1 (0.5%) in spring, summer, autumn and winter, respectively. The number and frequency of cases of anaphylaxis by gender and type of bee is shown in Table 1. Also, Figure 1 displays the Error bar of various bees (Table 1) (Figure 1).

Table 1. Number and frequency of cases of anaphylaxis by gender (male, female) and type of bee

Sex	Paper Wasp	Yellow jacket	Honey jacket	Unknown
Male	15 (11.6%)	37 (28.7%)	68 (52.7%)	**9** **(7%)**
Female	4 (5.6%)	33 (45.8%)	23 (31.9%)	**12** **(16.7%)**
Total	19 9.5%	70 34.8%	91 45.3%	**21** **10.4%**

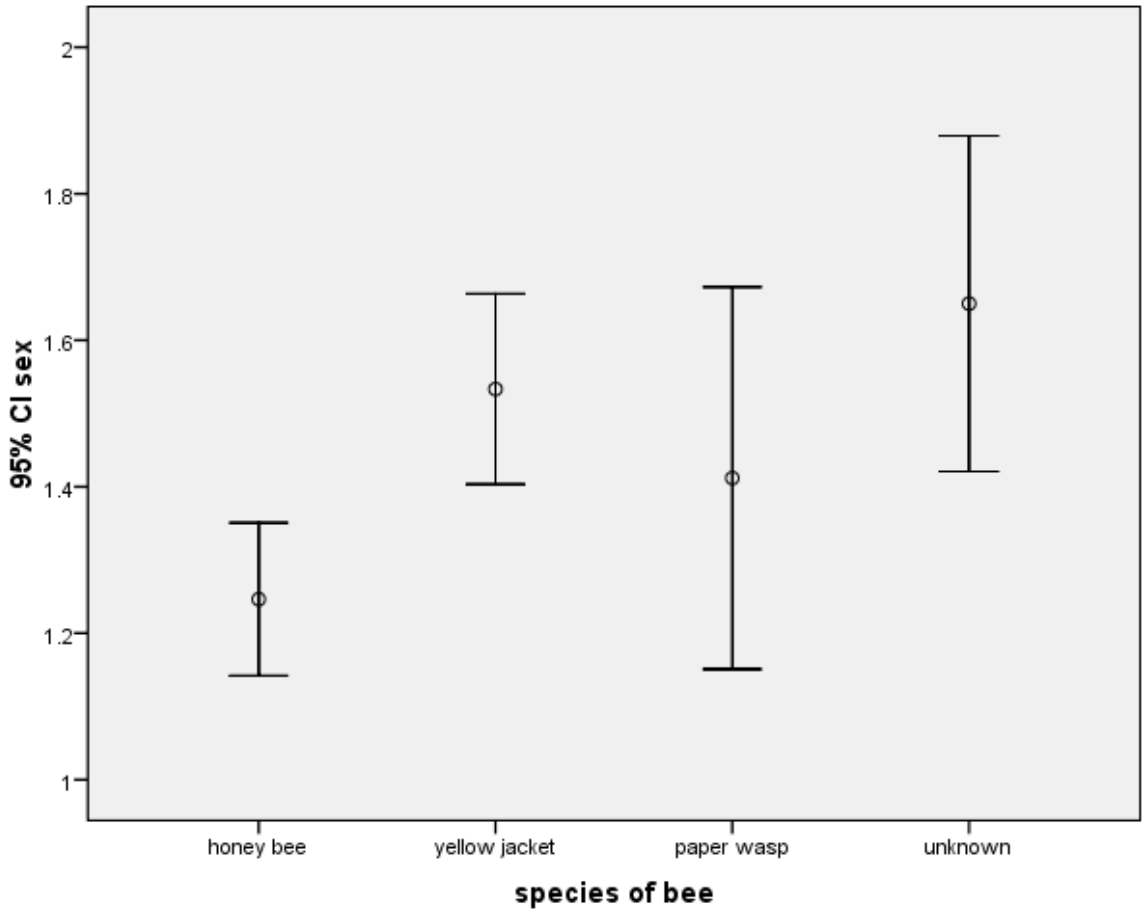

Fig 1. Frequency and 95% confidence interval of bees species involed in bee stings

91 (45.3%), 70 (34.8%), 19 (9.5%) and 21 (10.4%) had bites in each sex, which occurred between the type of bee and anaphylaxis abundance between the two sexes, the honey bee and yellow jacket stings male and female respectively and this difference is significant ($p = 0.003$). The number of patients with CPR by severity of disease and bee are given in Table 2.

Table 2: Number of patients with CPR by severity of disease and bee

		CPR	
		No	Yes
Mild	Honey bee	0	29
	Yellow jacket	0	25
	Paper Wasp	0	3
	Unknown	0	3
Moderate	Honey bee	0	14
	Yellow jacket	0	13
	Paper Wasp	0	6
	Unknown	0	4
Severe	Honey bee	0	20
	Yellow jacket	0	9
	Paper Wasp	2	1
	Unknown	0	6

As it is shown, anaphylaxis cases were significantly higher in spite of the small number of Paper Wasp stings (a total of 7 cases of CPR, $p = 0.01$).

In the present study, the frequency of anaphylactic reaction in studied patients was significantly higher during the day as opposed to night ($P = 0.05$). In addition, there were significant differences between the sting cases especially in case of male subjects and outdoors ($P = 0.007$). The most cases of bee stings and the subsequent anaphylactic reactions were observed in the extremities (108 cases; 53.7%), followed by the head and neck (48 cases, 32.9%). Most of the bee sting cases occurred at a significantly higher rate in the mornings and evenings (92.5%) and outdoors($P = 0.05$)(Table 3).

Table 3. Frequency distribution of bee sting among patients with anaphylactic reaction according their gender

		Male	Female	P-value
Number of bee sting	One time	62 (48.1)	30 (41.7)	0.41
	1-5 times	54 (41.9)	38 (52.8)	
	5-10 times	6 (4.7)	1 (1.4)	
	>10 times	7 (5.4)	3 (4.2)	
Bee sting place	Indoor	40 (51.3)	38 (48.7)	0.007
	Outdoor	79 (73.8)	28 (26.2)	
	Apiary	10 (62.5)	6 (37.5)	
Bee sting sites	Upper Extremities	69 (53.5)	39 (54.2)	0.001
	Lower Extremities	17 (13.2)	21 (29.2)	
	Head and Neck	37 (28.7)	6 (4/7)	
	Trunk	11 (15.3)	1 (1.4)	

According to patients' data registered in the above database, the most frequent symptoms were itching (79%), hives (68%), and pulmonary symptoms including cough, wheezing and dyspnea (54%), and palpitations and hypotension (37%). The most affected systems involved in the patients with anaphylaxis were as follows: skin (85.6%), respiratory system (87.6%), cardiovascular system (35.8%), nervous system (17.4%) and digestive system (10.9%). In addition, system involvement was significantly higher in adults than in pediatric patients (P=0.05) (Table 4 and 5).

Table 4.- frequency of bee sting symptoms in patients with anaphylaxis reaction

Symptom	**Frequency**	**%**
Pruritus	160	79
Urticaria	137	68
Cough/wheezing& Dyspnea	109	54
Hypotension	74	37
Angioedema	69	34
Laryngospasm	59	30
Rhinitis	52	25
Flushing	47	23
Nausea &headache	34	17
Gastrointestinal symptom	22	11
Throat clearing	14	7
Loss of consciousness	5	2.5

Conjunctival erythema	1	0.5

Table 5. Frequency of involved organs among patients with anaphylaxis reaction

	Adult	Pediatric	Total
Patients	169 (84.1%)	32 (15.9%)	201 (100%)
Skin	144 (83.7%)	28 (16.3%)	172 (85.6%)
Respiratory	133 (84.2%)	25 (15.8%)	158 (78.6%)
Cardiovascular	65 (90.3%)	7 (9.7%)	72 (35.8%)
Neurologic system	32 (91.4%)	3 (8.6%)	35 (17.4%)
Gastrointestinal	20 (9.1%)	2 (90.1%)	22 (10.9%)

In this study, a total of 7 cases (9.5%) out of 32 children with bee stings, and 67 cases (39.64%) out of 169 adults with bee stings experienced hypotension. The hypotension rate was significantly higher in adults than in pediatric patients with bee stings (P = 0.05). None of the children had a decreased level of consciousness in this research, but 6 (3.6%) of the adults did; however, there was no significant difference between children and adults in terms of the frequency of decreased consciousness level (P = 0.14). There was significant difference between the two genders in terms of incidence of anaphylactic reactions in the affected system (P = 0.01). In this study, 78 (38.8%), 107 (53.2%) and 16 (8%) of stings occurred indoors, outdoors and beekeeping areas respectively, and there was a significant difference between the two groups in terms of frequency severity of mild anaphylaxis in the stung organ (P = 0.001). In the present study, most cases of severe bee stings have been reported in the head, neck and upper extremities, which is statistically significant. In this study, 95% of the subjects experienced bee stings fewer than 10 times, and 80% of them had severe anaphylactic attacks after being stung more than 10 times and this difference was significant. Of all admitted cases, 58.3% were hospitalized for over 12 hours, and this difference was significant (P = 0.007) (Table 6).

Table 6. Frequency of bites and involved organs among patients with anaphylaxis reaction according disease intensity

		Mild	Moderate	Sever	P-value
Place of bites	Indoor	36 (46%)	26 (33.3%)	16 (20.5%)	0.001
	Outdoor	23 (20.6%)	43 (40.2%)	42 (39.3%)	
	Apiculture	2 (12.5%)	6 (12.5%)	8 (50%)	
Number of bites	<10	58 (30.4%)	75 (39.3%)	58 (30.4%)	0.003
	>10	2 (20%)	0	8 (80%)	
Body parts	Upper	35 (32.4%)	40 (37%)	33 (30.6%)	
	Lower	9 (23.7%)	17 (44.7%)	12 (31.6%)	
	Head and neck	15 (31.2%)	15 (31.2%)	18 (37.2%)	
	Trunk	1 (14.3%)	3 (42.9%)	3 (42.9%)	
Hospitalization hours	Without hospitalization	33 (46.5%)	20 (28.2%)	18 (25.4%)	0.007
	<4 hours	22 (20.6%)	48 (44.9%)	37 (34.6%)	
	4-10	3 (27.3%)	4 (36.4%)	4 (36.4%)	
	>10 hours	2 (16.7%)	3 (25%)	7 (58.3%)	

In this study, 132 (65.7%) of patients with anaphylactic shock used corticosteroid and antihistamine (P = 0.003). In addition, serum therapy was used for 40 of the patients (19.9%) with anaphylaxis shock in order to control the condition of the patients. There was a significant relationship between the use of serum therapy and the severity of anaphylactic reaction (P = 0.025). Although the patient's education is important and necessary, no effective measures are taken to carry out subsequent follow-ups and referral to an allergy specialist in this study conducted on patients registered in the studied database.

Discussion

This cross-sectional study was conducted to determine the epidemiological status of the prevalence of anaphylaxis to bee stings in rural areas of Gorgan district, north of Iran. The incidence of anaphylaxis in this study is reported to be equal to 1 in every 700 people, which was far higher than similar studies, such as a study conducted in the United Kingdom (1 in 1333). A. Helbing (2004) also reported an annual anaphylactic reaction prevalence rate of 7.9 to 9.6 per 100,000 people (6). In the present study, anaphylaxis was more prevalent in adults than children and the prevalence of anaphylaxis to bee stings was higher in both groups than that of Bemanian et al. (2007) (ranging from 0.4 to 4% of all cases of anaphylaxis) (7). The prevalence of anaphylaxis seems to vary according to gender and age depending on the study area, the duration and anaphylaxis symptoms based on the geographical location and subject selection. The results of the present study show that the prevalence of anaphylaxis is 61.6% and 37.9% in males and females, respectively, which was more prevalent in male adults and children. Most patients were also male in the Alvarez-Twose et al.'s study (2013), the aim of which was to investigate patients with anaphylaxis to bee stings and mastocytosis (7). In another similar study, Linard et al. (2014) reported the highest cases of anaphylaxis in men, mainly in the head and neck areas (8). In a study titled the prevalence of anaphylaxis in Tasmania, Australia, Blackhall et al. (2015), reported that 78.9% of adults and 21.7% of children were affected. However, unlike the results of our study, the prevalence of anaphylaxis in adult women was higher than that of men (9). It seems that as more men are present

in open environments and carry out jobs such as farming and bee-keeping, they experience more bee stings. The higher number of anaphylaxis incidents as a result of being stung in the upper extremities, such as the head and neck, can be due to the fact that these body parts were not covered and thus were exposed to bee stings more frequently as most bees come in contact to these areas whilst flying. The highest sting cases occurred at noon and afternoon, which can be mainly due to the fact that bees are more active during the day, as a result, there is more exposure to bee sting occurring at these times. Moreover, higher temperatures during the day may make the bees more irritated.

The findings of the present study also revealed that skin, respiratory, cardiovascular and neuronal involvements were the most common symptoms of the patients, respectively. Similar to the results of the present study, Xie C et al.(2013), showed in their study that head and neck areas and upper extremities were the most affected areas (10). The results of this study were also consistent with Nabavi et al.'s study (2017), which was performed by registeringthe diagnostic and therapeutic characteristics of patients with anaphylaxis caused by any agent during 2012-2015 in three university hospitals in Tehran, Iran. Similar to our study, their results also showed the skin, respiratory, cardiovascular and nervous systems as being the most commonly involved organs, respectively (11). The anaphylaxis-related skin symptoms were also prevalent in the present study, which is consistent with Lieberman P's study, and affects up to 80% of the cases (12). Respiratory complaints account for about half of the reactions in children and adults. Golden et al., reported in a study on patients with anaphylaxis caused by bee sting, that skin, cardiovascular and respiratory systems were the most involved, and the nervous and digestive systems' involvement was sometimes observed (13).

A total of 19.9% of patients with anaphylactic reactions in the above study received intravenous liquids and as the patients stated, 65.7% of them had been injected with antihistamines and corticosteroids and epinephrine was injected only to 5% of patients. Gelincik also showed that only 2.3% of patients needed epinephrine for treatment, which is similar to our results (14, 15). The results of a study conducted by Canadian physicians showed that 76% of them did not know the epinephrine injection dose, and only 25% of them knew about the stages of epinephrine injection, which are similar to the present study (16). It seems that most patients and even physicians are not aware of the importance of using epinephrine as an effective treatment, where if used promptly and with the correct dosage, can be a life-saving treatment. According to patients, in some cases physicians residing in the treatment centers have also refused to give injections of an epinephrine prescribed by the allergy specialist to be injected in case of anaphylaxis. In addition, most patients were not well informed about the importance of epinephrine injections in the case of anaphylactic reactions. This can be justified by pointing to the fact that the epinephrine injection is scarce and also doctors' fears regarding the epinephrine administration has pushed the patients towards a non-use strategy. These surveys reveal that medical staffs have inadequate knowledge about the treatment of anaphylaxis and training of patients, conducting workshops and holding retraining sessions for physicians and other health professionals can improve their level of knowledge as well as the patients' health status.

In this study, the occurrence of anaphylaxis with honey bee and Yellow jacket was higher than other bees. There was also a significant difference between bee and sex, where women were more likely to be stung by a yellow jacket and go into anaphylaxis. Regarding the type of bee and the severity of the occurrence of anaphylaxis in patients, the most severe cases have occurred in the

studied area and have a significant difference (p = 0.007). Gelincik et al surveyed the prevalence of allergy to the honey bee in adults in the busy Eurasia area, which is the most frequent type of bee stings (19). Our study was based on a patient's history of experiencing one bee sting (45.8%), in contrast to their study which recorded more than 56.3% of patients having been stung more than once. However more than 54.2% of patients had a history of multiple bee stings and were not referred to an allergy specialist after the first systemic response for diagnostic and therapeutic work.

Almost half of the patients were admitted to the emergency department, which is very similar to our study. Only about one-tenth of them received adrenaline in the emergency department. None of the patients were examined, received immunotherapy or referred to an allergy specialist. Similar to this study, the most important agent of the defendant has also been reported (١٦). Based on the results of this study, it was observed that anaphylaxis was more severe in the Paper Wasp stings than other bees, and also the incidence of CPR cases, despite the small number, was caused by Paper Wasp stings, which is also significant (p = 0.01).

One of the limitations of this study was using the history of previous cases of bee stings in health houses،and our results can be affected by the recall bias.

Moreover despite there being a number of questions in the questionnaire regarding patients' education requirements, subsequent follow-ups and referrals to an allergy specialist, they were not completed adequately. Even more none of the cases were referred to an allergy specialist (even if they had experienced more than one anaphylactic event)..

Conclusion

The bee sting-induced anaphylaxis can be deadly, if not treated correctly and on time. Based on our study, case finding was successful through the rural health network. In order to obtain accurate epidemiological information on the prevalence of anaphylaxis due to bee stings, an anaphylaxis registry and healthcare service packages are recommended. In this integrated model, raising people awareness and the introduction of a guideline for treatment of anaphylaxis by the community health workers is suggested. It seems that good steps can be taken in promoting the health status of these patients by providing needed medicines such as epinephrine injections and the immunotherapy vaccine for bee stings while providing insurance coverage for patients who receive immunotherapy.

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