PAEDIATRICS

Clinical Predictors for Systemic Reaction in Children with Hymenoptera Sting: A Southeast Asian Experience

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ABSTRACT

Introduction: **Insect bites and stings are common in the paediatric age group. Hymenoptera stings (hornets, wasps, bees and ants) are the leading cause of insect anaphylaxis. The post-envenomation severity varies and is unpredictable, ranging from local to severe systemic reactions. This study aimed to explore the prevalence and predictors of severe systemic reactions post Hymenoptera stings.**

Methods: **A retrospective review of the medical records of paediatric patients with Hymenoptera stings, admitted to two major tertiary centres from January 2014 to December 2018, was conducted. Baseline characteristics, including age, positive history of atopy, type of insects, clinical manifestations (localised or systemic) and complications, were documented. The prevalence of systemic reaction was determined using descriptive statistics. Simple logistic regression and multiple logistic regression were used to determine the factors causing systemic reaction among children with alleged Hymenoptera stings.**

Results: **There were 459 children in the study, predominantly male (n = 300 (65.4%)). The prevalence of systemic reaction in our cohort was 24.8% (n = 114). The majority of cases were hornet stings (n = 333), followed by bees (n = 78), wasps (n = 26) and ants (n = 22), respectively. Older children (OR = 1.13, 95% CI: 1.07-1.19), history of allergy (OR = 4.16, 95% CI: 1.86-9.29), history of atopy (OR = 2.77, 95% CI: 1.49-5.15), and number of sting (OR = 1.08, 95% CI: 1.01-1.15) were associated with higher likelihood of systemic reaction.**

Conclusion: **Older children with a history of allergy or atopy and more stings were identified as increased risk factors for developing systemic reactions.**

KEY WORDS

Hymenoptera, hornet, allergy, systemic reaction, children

INTRODUCTION

Children are susceptible to being bitten and stung by insects due to their curious nature and outdoor playtime. Most insects are not poisonous, but some may cause a wide range of reactions in response to envenomation. Of all insect orders, Hymenoptera sting is the leading cause of allergic reactions[1)]. The reaction dimension varies from mild local reaction to severe systemic reaction anaphylaxis that may even lead to death. Insect sting is the second-most common cause of anaphylaxis after food allergy, about 20% of which results in mortality[2)].

Hymenoptera venom contains various chemical substances that may cause local injury to the surrounding tissues and even damage other organs through direct action. There is no single predictive or diagnostic value to predict the severity of reaction in children[3)]. Hymenoptera is an order that includes hornets, wasps, sawflies, bees and ants. Its etymology originates from a Greek word, *hymen* means membrane and *pteron* indicates wing. The species vary by continent, as each of them carries different genetic materials[4)]. Hymenoptera is vital for the ecosystem, as many of them are pollinators to flowers, food crops and fruit trees. In Malaysia, more than 58 species have been described under this order[4)]. Some are pests to some crops, but most are beneficial and essential for humans[5)]. Bees, wasps and hornets have stings on their abdomen for self-defence or to paralyse their prey.

The most clinically significant effect of multiple stings is immune-mediated hypersensitivity, particularly Immunoglobulin E (IgE) - mediated reaction and systemic response. However, an anaphylactic reaction does not rely on the number of stings. The shorter the duration from envenomation to emergence of symptoms, the more severe the systemic response may be[7,8)]. The risk of repeated systemic reaction is much lower in children, ranging around 10-20%, and repeated reaction is usually less severe than earlier envenomation[6)]. The estimated lethal dose in humans is 500 stings for adults or about 20 stings/kg in most mammals[7)]. Less severe reactions are observed in younger paediatric patients compared to adults[3,8)]. This study aimed to determine the risk factors in children with Hymenoptera sting and predisposing factors for severe systemic reaction.

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Table 1: Demographic characteristics of children (N = 459).

Variables	n (%)
Age (Years)	5.69 (4.13)[a]
Sex	
Male	300 (65.4)
Female	159 (34.6)
Race	
Malay	455 (99.1)
Non-Malay	4 (0.9)
Types of Hymenoptera	
Hornet	333 (72.5)
Wasp	26 (5.7)
Bee	78 (17.0)
Ant	22 (4.8)
History of allergy	
No	427 (93.0)
Yes	32 (7.0)
History of atopy	
No	403 (87.8)
Yes	56 (12.2)
Family history of atopy	
No	424 (92.4)
Yes	35 (7.6)
History of previous exposure	
No	441 (96.1)
Yes	18 (3.9)
Site of sting[c]	
Head	218/459 (47.5)
Trunk	66/459 (14.4)
Limbs	327/459 (71.2)
Number of stings	1.00 (2.00) [b]
Time from alleged to presentation (hours)	1.80 (2.25) [b]

[a]mean (SD), [b]median (IQR), [c]For site of sting, the total percentage is more than 100% as one patient can have more than 1 location of sting.

METHODS

This was a retrospective study of patients medical records admitted to two tertiary hospitals along the Malaysian east coast for Hymenoptera stings from January 2014 to December 2018. Records of patients below 18 years of age who sought medical attention were included in the study. The types of stings were based on patients and/or family members self-reports. Epidemiological data (age, gender and race), clinical features, treatment given, and outcome were recorded. The study received approval from the Human Research Ethics of the university and Ministry of Health (USM/JEPeM/19120946).

In this study, systemic reactions are defined as the presence of at least one of the symptoms or signs of anaphylaxis. It may involve many systems, such as skin, and may present with feelings of warmth, flushing, urticaria, angioedema and respiratory symptoms, such as nasal itching, congestion, sneezing, rhinorrhoea, itching of throat, dysphonia, hoarseness, stridor, dyspnoea, chest tightness, cough and wheezing. Gastrointestinal system signs and symptoms are nausea, vomiting, dysphagia and diarrhoea. The cardiovascular system's involvement may present with faintness, dizziness, syncope, chest pain, palpitation, dysrhythmia, hypotension and even cardiac arrest. Neurological manifestations of anaphylaxis include anxiety, seizures, headache and confusion; in younger children, there may be sudden behavioural changes. Patients may also present with periorbital itching, erythema and oedema[9]. Allergy is a body's immune response to a foreign substance known as an allergen. It is mediated by immunoglobulin E, which triggers the cells to produce a chemical substance to protect the body from the allergen[10]. Atopy is a group of diseases that share an underlying problem in the immune system. It includes bronchial asthma, allergic rhinitis and eczema. History of previous exposure is defined as previous exposure to the same order of Hymenoptera.

Patients are considered to have anaphylaxis if they present acutely with any of these three criteria:[9]

1) Acute onset of a reaction involving the skin, mucosal tissue or both, whereby the patient may present with urticaria, pruritus, flushing or angioedema. In addition, they should exhibit at least one of the following symptoms:

a) Respiratory symptoms, such as stridor, shortness of breath, wheezing or bronchospasm
b) Cardiovascular symptoms, such as hypotension or signs of end-organ dysfunction

2) Presence of two or more of the following reactions after being exposed to an allergen:

a) Skin manifestation
b) Respiratory symptoms
c) Cardiovascular symptoms
d) Gastrointestinal symptoms, such as excessive salivation, vomiting or abdominal pain

3) Hypotension alone after exposure to an allergen.

Statistical Analysis

Statistical analysis was done using the SPSS version 27.0. Descriptive analyses are expressed as frequencies, means ± standard deviation, counts and percentages, as appropriate. ANOVA, Chi-square, Kruskal-Wallis, simple and multiple logistic regression tests were conducted to compare and identify the factors for systemic reaction. A p-value of < 0.05 was taken as significant for all statistical analysis in this study.

RESULTS

A total of 459 children with Hymenoptera stings were included in the study, with a mean age of 5.69 (± 4.13) years old and the majority were male, as shown in Table 1. The youngest age documented in our study was 7 days old, and the oldest was 17.7 years old. The majority of cases were hornet stings (n = 333), followed by bees (n = 78), wasps (n = 26) and ants (n = 22), respectively. The events mostly occurred outdoors (61.7%). Most patients (50.5%) sought medical attention within the first hour of envenomation. In our cohort, 12.2% of patients had various types of atopy symptoms, 7.6% had a family history of atopy and 3.9% had a history of previous exposure to the same Hymenoptera order. A total of 274 (59.7%) patients had a single sting by Hymenoptera. The most common sites of stings were at the limbs (71.2%), followed by the head (47.5%) and torso (14.4%). The complications observed included renal injury, rhabdomyolysis, liver injury, coagulopathy and anaphylaxis. Anaphylaxis was the main complication that developed in 64 cases, followed by coagulopathy in 37 cases. There was 1 isolated complication with liver injury and 2 children with rhabdomyolysis, of which 1 developed acute renal injury requiring haemodialysis. No death reported in our study.

Table 2 depicts the clinical profile of children with specific types of Hymenoptera stings. The proportion of patients with a history of allergy and atopy and family history of atopy was higher in the wasp sting group compared to the other Hymenoptera group. Most patients were stung on limbs, but most of the wasp cases were stung at the head area. Looking at the mean time from alleged sting/bite to presentation to medical providers, children bitten in the ants group were the earliest to seek treatment after the event occurred (1.58 hours), followed by hornets (1.73 hours), bees (2.63 hours) and wasps (2.70 hours). Among the different Hymenoptera groups, those stung by wasps presented a higher percentage of developing systemic reaction (50%), followed by bees (25.6%), hornets (23.1%) and ants (18.2%).

Simple logistic regression analysis, as demonstrated in Table 3, showed multiple factors associated with systemic reaction among children with Hymenoptera stings. Factors that increased the likelihood of developing systemic reaction were older age (OR = 1.17, 95% CI: 1.11-1.23), wasp stings (OR = 3.33, 95% CI: 1.48-7.47), a history of allergy (OR = 5.9, 95% CI: 2.73-12.52), a history of atopy (OR = 3.38, 95% CI: 1.90-6.01), a family history of atopy (OR = 3.18, 95% CI: 1.58-6.42) and more than 1 sting (OR = 1.10, 95% CI: 1.03-1.17).

We performed multiple logistic regression analysis, as shown in Table 4, after excluding the possible interaction and multicollinearity

Table 2: Clinical profile of children with a specific type of Hymenoptera sting (N = 459).

Variable	Hornet (n = 333)	Wasp (n = 26)	Bee (n = 78)	Ant (n = 22)	P-value
Age (Year)[e]	5.73 (4.07)	6.62 (3.52)	4.74 (4.31)	7.41 (4.52)	*0.026[a]
Sex (Male)	226 (67.9)	20 (76.9)	42 (53.8)	12 (54.5)	*0.043[c]
History of allergy	18 (5.4)	6 (23.1)	5 (6.4)	3 (13.6)	**0.009[d]
History of atopy	36 (10.8)	7 (26.9)	10 (12.8)	3 (13.6)	0.123[d]
Family history of atopy	21 (6.3)	4 (15.4)	8 (10.3)	2 (9.1)	0.175[d]
Previous exposure	7 (2.1)	1 (3.8)	6 (7.7)	4 (18.2)	**0.002[d]
Number of stings[f]	1.00 (2.00)	2.50 (6.00)	1.00 (1.00)	1.00 (1.00)	**0.003[b]
Location of sting					
Head	159 (47.7)	19 (73.1)	37 (47.4)	3 (13.6)	***0.001[c]
Body	56 (16.8)	4 (15.4)	3 (3.8)	3 (13.6)	*0.014[d]
Limb	237 (71.2)	18 (69.2)	55 (70.5)	17 (77.3)	0.935[c]
Time to presentation (Hour)[f]	1.73 (1.73)	2.70 (4.25)	2.63 (7.77)	1.58 (3.05)	*0.040[b]
Systemic reaction	77 (23.1)	13 (50.0)	20 (25.6)	4 (18.2)	*0.030[c]

[a] one-way analysis of variance. [b] Kruskal-Wallis H test, [c] χ^2 test, [d] Fisher exact test.

All variables are expressed as number and percentage, except for age (presented as mean and SD), number of stung and time to presentation (presented as median and IQR).[e]mean (SD), [f]median (IQR).

Table 3: Simple logistic regression of factors associated with systemic reaction among children with Hymenoptera sting (N = 459)

Variables	No SR, n = 345	SR n = 114	Crude OR (95% CI)	P-value
Age (Year)[a]	5.05 (3.72)	7.66 (4.67)	1.17 (1.11, 1.23)	***< 0.001
Sex				
Male	216 (72.0)	84 (28.0)	1.67 (1.05, 2.68)	*0.032
Female	129 (81.1)	30 (18.9)		
Types of Hymenoptera				
Hornet	256 (76.9)	77 (23.1)		
Wasp	13 (50.0)	13 (50.0)	3.33 (1.48, 7.47)	**0.004
Bee	58 (74.4)	20 (25.6)	1.15 (0.65, 2.02)	0.638
Ant	18 (81.8)	4 (18.2)	0.74 (0.24, 2.25)	0.594
History of allergy				
No	333 (78.0)	94 (22.0)		
Yes	12 (37.5)	20 (62.5)	5.90 (2.73, 12.52)	***< 0.001
History of atopy				
No	316 (78.4)	87 (21.6)		
Yes	29 (51.8)	27 (48.2)	3.38 (1.90, 6.01)	***< 0.001
Family history of atopy				
No	327 (77.1)	97 (22.9)		
Yes	18 (51.4)	17 (48.6)	3.18 (1.58, 6.42)	***0.001
History of previous exposure				
No	335 (76.0)	106 (24.0)		
Yes	10 (55.6)	8 (44.4)	2.53 (0.97, 6.57)	*0.057
Site of sting: Head				
No	189 (78.4)	52 (21.6)		
Yes	156 (71.6)	62 (28.4)	1.45 (0.94, 2.21)	0.090
Site of sting: Trunk				
No	299 (76.1)	94 (23.9)		
Yes	46 (69.7)	20 (30.3)	1.38 (0.78, 2.46)	0.268
Site of sting: Limb				
No	94 (71.2)	38 (28.8)		
Yes	251 (76.8)	76 (23.2)	0.75 (0.48, 1.18)	0.214
Number of stings[b]	1.00 (2.00)	1.50 (2.00)	1.10 (1.03, 1.17)	*0.003

SR = systemic reaction.

All variables are expressed as number and percentage, except for age (presented as mean and SD), number of stung and time to presentation (presented as median and IQR).[a]mean (SD), [b]median (IQR)

Table 4: Multiple logistic regression of factors associated with systemic reaction among children with Hymenoptera sting

Variables	No SR, n = 345	SR, n = 116	Adj. b (SE)	Adj. OR (95% CI)	P-value
Age (Years)[a]					
	5.05 (3.72)	7.66 (4.64)	0.12 (0.03)	1.13 (1.07, 1.19)	***< 0.001
History of allergy					
No	333 (78.0)	96 (22.0)	Ref		
Yes	12 (37.5)	20 (62.5)	1.43 (0.41)	4.16 (1.86, 9.29)	***< 0.001
History of atopy					
No	316 (78.4)	89 (21.6)	Ref		
Yes	29 (51.8)	27 (48.2)	1.02 (0.32)	2.77 (1.49, 5.14)	***0.001
Number of stings[b]	1.00 (2.00)	1.50 (2.00)	0.07 (0.03)	1.08 (1.01, 1.15)	*0.025

All variables are expressed as number and percentage, except for age (presented as mean and SD), number of stung and time to presentation (presented as median and IQR).[a]mean (SD), [b]median (IQR).

Forward LR method was applied. Constant = -2.35. Cox & Snell R Square = 0.127. Classification table overall percentage of correct prediction = 78.2%. Hosmer and Lemeshow Test χ^2 (8) = 8.41, p = 0.394. Area under receiver operating characteristics curve = 72.1% (95% CI: 66.2% to 78.0%). There are no multicollinearity and no interaction between variables included. The data does not contain any influential outlier.

SR: Systemic reaction. Adj.: Adjusted. OR: Odd ratio.

between the variables and demonstrated that a history of allergy and of atopy increased the likelihood of systemic reactions by 4.16 (95% CI: 1.86-9.29) and 2.77 (95% CI: 1.49-5.14), respectively. Age and number of stings increased the likelihood of developing systemic reaction by 1.13 (95% CI: 1.07-1.19) and 1.08 (95% CI: 1.01-1.15), respectively.

DISCUSSION

To our knowledge, no study in Southeast Asia compares the outcomes of different types of Hymenoptera and the risk factors contributing to systemic reactions in the paediatric age group. Most studies have explored clinical response and systemic reaction after various Hymenoptera envenomation; however, they mostly involved adult patients, and the information available for the paediatric age is scarce. There are over 150,000 living species of Hymenoptera worldwide[11]. Our cohort age demonstrated that children below 13 years old comprised 92% of total cases, and majority were dominated by boys in which consistent with similar studies in Turkey, the United States, Thailand and Ireland[3,12-15]. This is possibly due to them being more adventurous and highly curious and their risk-taking behaviour. We also observed fewer cases in older children, reflecting the greater maturity with increasing age. Moreover, boys usually spend more unsupervised time outside with friends compared to girls[16].

Almost 62% of cases occurred outdoors, which is expected as Hymenoptera generally sting when they feel threatened, especially when the threat involves their colonies, which are more often found outdoors. The Hymenoptera nest may occasionally be found indoors, and although relatively less common, a single Hymenoptera passing by may also sting if it feels threatened and cannot avoid combat.

Upon closer inspection of the pattern of stings, the number of incidents was consistently higher between April and September for all years (data not shown in the result) which correspond to warm and sunny season in this region. It is worth noting that mean monthly precipitation was significantly higher from November to January in the region[17]. This feature is consistent with the fact that Hymenoptera spend more time outside their hives during sunny season to seek food[13,18]. Another important point is that the peak time of Hymenoptera sting incidents was 6 pm, which far exceeded other times of the day. This is probably because it is the best time for children from both regions to play outdoors.

Our data showed that most patients sought medical attention within the first hour of envenomation. This shows that parents are mindful of the danger and are concerned about the pain that the child has to bear. However, this does not really reflect the exact number of cases because this data was acquired only from those who sought medical attention. Notably, there is a small percentage of people who prefer home remedies and traditional medicine in treating Hymenoptera stings.

In our cohort, almost 25% of children demonstrated the presence of systemic reaction post Hymenoptera sting. The figure is relatively higher than studies conducted in other regions, such as Ireland, Israel and Turkey, with the systemic reaction prevalence ranging from 0.4-16%[3,13]. The difference may be due to the way the study was conducted, where all of our samples were victims of Hymenoptera stings, while the studies conducted elsewhere were questionnaires distributed randomly among school children. The discrepancy may also be attributed to victims who did not seek medical attention or opted for alternative treatment post-Hymenoptera stings due to mild or no reaction, resulting in an overestimation of the prevalence of systemic reactions in our study. Cutaneous symptoms (19%) predominate others in systemic manifestation, followed by gastrointestinal (7.6%), respiratory (7.4%), ocular (5.9%), cardiovascular (2.8%), oral (2.6%) and neurological (2.4%) symptoms. This is consistent with other studies that reported the highest prevalence to be of cutaneous symptoms[3,12,19].

We also demonstrated that older children were more prone to systemic reactions, with the mean age of the systemic reaction being around 8 years ($p < 0.001$). A few other studies also found similar results, where older children are more prone to more severe systemic reactions compared to a younger age[3,12]. This may be due to the immaturity of the immunologic response in the younger age group. Nevertheless, a retrospective study conducted in Thailand found that children younger than 15 years were more likely to have systemic reactions[16]. However, the study was not exclusively for the paediatric age group, as the sample involved adults as well. This clinical manifestation pattern differ from food allergy reaction e.g peanut whereby the younger age group demonstrated more severe systemic reaction compared to older children[20].

Our data showed that more than 60% of children with a history of allergy developed systemic reactions post envenomation of Hymenoptera sting. Similarly, those with a history and family history of atopy had a 50% chance of developing systemic reaction. These findings align with other studies that found that a history of atopy is associated with systemic reactions in Hymenoptera stings[3,16]. Even though our study had a relatively larger sample, the sample was mostly from a single race in the majority of cases and homogenous. Hence, it may not represent the entire country's population, with mixed races and ethnicity. Interesting concept of biphasic anaphylaxis post bee/wasp stung as highlighted by Nagamine describing on reappearance of the clinical symptoms despite complete resolution of the initial reaction[21]. It was proposed the early administration of epinephrine may prevent the complication. Fortunately, in our cohort the standard guidelines for all patients with anaphylaxis or even impending clinical reactions of anaphylaxis were immediately given epinephrine intramuscularly in the majority of the cases. Hence, such phenomenon were not encountered in our cohort.

In conclusion, older children and a positive history of allergy and atopy were found to be significantly associated with systemic reaction post Hymenoptera sting.

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