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The etiology, risk factors, and clinical features of anaphylaxis: The single-center retrospective cohort study of the tertiary university hospital

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Ethics Committee Approval
The study was approved by Sivas Cumhuriyet University's non-interventional clinical research ethics committee, with the decision number 2020-01/01, dated January 15, 2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Anaphylaxis presents in multiple ways, making its diagnosis challenging. Delayed diagnosis can lead to a postponement in administering crucial adrenaline treatment. The prevalence of anaphylaxis varies by geographical region and gender. However, there has been no comprehensive regional analysis of anaphylaxis data within our country. Despite an increasing incidence, our understanding of anaphylaxis etiology, risk factors, and clinical features remains limited, particularly within our nation. This study aims to assess the frequency, etiology, risk factors, and clinical findings of anaphylaxis among patients seen at the allergy clinic of a tertiary university hospital. Additionally, it seeks to compare regional data with existing literature.

Methods: This retrospective cohort study reviewed the medical records of 8,295 patients who visited the allergy outpatient clinic at Sivas Cumhuriyet University Hospital between July 2, 2018, and December 10, 2019. The hospital's data system retrospectively analyzed records using the ICD code T78.2 (anaphylaxis). Only cases where patients were prescribed an adrenaline auto-injector were included. The study evaluated anaphylaxis frequency, etiologies, demographics, and clinical features.

Results: The study identified 77 patients (n=77) with a mean age of 40.29 (3.77) years, consisting of 47 females and 30 males. The frequency of anaphylaxis among allergy outpatient admissions was less than 1% (0.009%). Single-type atopic diseases included venom allergy (23%), drug allergy (14%), inhalant allergens (n=6), food allergens (n=4), and skin allergic diseases (n=3). Multiple allergic diseases were present in 40% (n=31) of cases. Prick tests were performed on 56 (72%) patients, with 25 (44%) yielding negative results. Among positive prick test cases, venom was the main cause of anaphylaxis (82%), while drug allergy was more prevalent (68.2%) among negative test results (P=0.016). Inhalant allergen sensitivity and allergen polisensitivity did not significantly influence the anaphylaxis cause (P<0.001). Causes of anaphylaxis included drug allergy (47%), venom allergy (31%), food allergens (16%), food-dependent exercise-induced reactions (n=2), idiopathic cases (n=2), and cold urticaria (n=1). Non-steroidal anti-inflammatory drugs (NSAIDs) (44%) and beta-lactams (10%) were the primary culprits. In cases where neither drugs nor venom were involved, food allergies were the cause (P<0.001). With venom allergy, the cause was venom, and without venom, drug allergy was the cause (P<0.001). Female patients showed significantly higher drug- and food-related anaphylaxis rates than males (P=0.032 and P=0.042, respectively). History of *Apis mellifera*-related anaphylaxis was significantly more common than *Vespula vulgaris*-related cases (P=0.028). Anaphylaxis severity included grade 2 (30%), grade 3 (48%), and grade 4 (12%) reactions. Recurrent anaphylaxis episodes occurred in 55% (n=42) of patients. Initial hospital administrations involved epinephrine injections in only 25% (n=19) of cases. Cutaneous symptoms were present in 94%, respiratory symptoms in 88%, cardiovascular symptoms in 63%, neurological symptoms in 57%, and gastrointestinal symptoms in 12% of patients.

Conclusion: This study identified drug allergy as the leading cause of anaphylaxis in the examined cases. Preventable factors contributing to drug-induced anaphylaxis included insufficient patient and physician knowledge and widespread over-the-counter drug use without medical consultation. Despite 55% of patients experiencing recurrent attacks, only a quarter received epinephrine administration. These findings emphasize the need to educate patients with recurrent anaphylaxis about avoidance strategies and to enhance healthcare providers' understanding of anaphylaxis treatment.

Keywords: etiology, frequency, anaphylaxis, hypersensitivity reactions

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Introduction

Anaphylaxis represents a swiftly advancing and potentially life-threatening systemic allergic reaction. Its immediate diagnosis and prompt treatment are imperative, yet it can be overlooked due to diagnostic challenges. Globally, the prevalence and incidence of allergic diseases are rising [1,2]. The causative factors and clinical manifestations of anaphylaxis exhibit variability. Shortcomings and delays persist in diagnosing and treating this condition within the realm of healthcare providers [2]. Conducting regional and national studies can enhance awareness among healthcare services, physicians, and the general public about anaphylaxis diagnosis and treatment [3,4].

Research on anaphylaxis has predominantly taken place in Western nations, often involving the analysis of hospital records, regional health data, or examining prescriptions for adrenaline auto-injectors [5-7].

The prevalence of anaphylaxis exhibits variations based on geographic regions and genders. However, a comprehensive analysis of anaphylaxis data within our country on a regional level has not been conducted. Our operational area represents a region where allergy immunology experts are not frequently available. The services of the respective specialized branch are only accessible when assigned by the Ministry of Health. If the designated specialist is unavailable, cases are typically referred to other regional hospitals for evaluation following initial treatment in emergency departments. With the recent assignment of an allergist to the Sivas province during the specified period, cases are retained within our region, establishing region-specific records.

Comprehending the causative factors, prevalence, and triggers of anaphylaxis holds significant importance for accurate patient treatment, preventing the recurrence of anaphylactic episodes, and devising preventive measures.

Our study endeavors to comprehensively depict anaphylaxis cases within the northeastern region of our country, meticulously scrutinizing the clinical and demographic attributes, as well as anaphylactic episodes among individuals prescribed adrenaline auto-injectors. Additionally, we seek to discern distinctive regional traits associated with these cases.

Materials and methods

The medical records of 8295 patients above the age of 16, who sought treatment at the outpatient clinic of the Department of Chest Diseases, Division of Allergy and Clinical Immunology, Sivas Cumhuriyet University Faculty of Medicine, between July 2, 2018, and December 10, 2019, due to anaphylaxis, were analyzed to establish a retrospective cohort using the hospital data system.

In our single-center cohort study, we retrospectively reviewed the hospital data system using the ICD-10 code T78.2 (anaphylaxis). Only instances where patients were prescribed the adrenaline auto-injector were included.

Our study encompassed the hospital records of all individuals who presented at the allergy clinic within the designated timeframe. Periods preceding and succeeding this window were excluded due to the allergist's exclusive association with the relevant center during this period. The EAACI 2021 anaphylaxis guideline (update) served as the basis for determining the inclusion criteria for our cases [2].

To diagnose anaphylaxis, it is necessary to fulfill one of the three primary clinical criteria. The most easily recognizable is the inclusion of one of these systemic presentations (such as respiratory, cardiovascular, neurological, or gastrointestinal symptoms) in conjunction with skin signs like acute onset urticaria, angioedema, and flushing. The second diagnostic criterion entails acute involvement in two systems following exposure to a recognized allergen (involving the skin, respiratory, cardiovascular, neurological, or gastrointestinal systems). The third and final diagnostic criterion involves the onset of acute hypotension after exposure to a known allergen, specifically characterized by a systolic blood pressure reduction to below 90 mmHg or a decrease of more than 30% from baseline in adults [2].

The same allergist evaluated all these patients. Conditions encompassing the differential diagnosis of anaphylaxis were ruled out through comprehensive anamnesis, thorough examinations, and laboratory tests.

However, given that the diagnosis of anaphylaxis was primarily clinical, meticulous attention was dedicated to the differential diagnosis process. This encompassed a comprehensive assessment of potential alternative diagnoses. The complete differential diagnosis included a sequential evaluation of allergic conditions (variants of urticaria, asthma), followed by respiratory and upper respiratory tract conditions (chronic lung disorders and upper respiratory tract diseases), cardiovascular disorders (vasovagal syncope, arrhythmias), endocrine disorders (hypo-hyperthyroidism, hypoglycemia), neuro-psychiatric conditions, toxic factors (such as scombroid poisoning), and pharmacological reactions. This evaluation was supported by various accessible laboratory tests (including complete blood count, liver and kidney function tests, TSH, and blood glucose levels), electrocardiography, abdominal ultrasonography, bidirectional chest X-ray, and pulmonary function tests.

Nonetheless, given that patients were not under direct observation during the episodes of anaphylaxis, diverse approaches were employed for recording, contingent upon the underlying causes. These methods encompassed relying on the patient's verbal account, consulting the records from the emergency department or medical teams, and when patients granted consent, accessing individual electronic medical record systems to gather details regarding their medical history and potential triggers.

Initially, we assessed the prevalence of anaphylaxis within the patient population under study. Subsequently, a comprehensive questionnaire was employed to scrutinize the demographic details found in the hospital records. This encompassed information such as the patient's gender, age, presence of atopic diseases, pre-existing chronic conditions, ongoing medication regimens, clinical manifestations of anaphylaxis, specifics of the triggering agent, clinical indications (about the affected organ systems), duration of hospitalization, and the therapeutic approaches employed. These details were meticulously documented alongside case report forms, which were gathered from hospital records in a cross-sectional and retrospective manner.

Anaphylaxis was classified into four grades following the Mueller classification [8]. Due to unmet conditions, provocation tests could not be conducted using the triggering agents (e.g., drugs, venom, and foods). Instead, skin prick tests were administered employing standardized allergen extracts of venoms (*Apis mellifera* and *Vespula vulgaris*), foods, inhalant allergens, and latex from ALK–Abelló*.

Ethics committee approval

Ethics approval and written informed consent was procured in accordance with ethical standards. The study received approval from the non-interventional clinical research ethics committee of Sivas Cumhuriyet University, under decision number 2020-01/01, dated January 15, 2020.

Statistical analysis

The data were presented as frequency (number and percentage) and mean (range) as applicable. Fisher's exact and chi-square tests were employed for 2 × 2 comparisons involving categorical variables. For numerical variables with counts below 30, the Mann-Whitney U and Kruskal-Wallis H tests were utilized for comparisons. All statistical analyses were conducted using SPSS software, version 23 (SPSS Inc., Chicago, IL, USA). Results with a *P*-value below 0.05 were considered statistically significant.

Results

Study group and the frequency of anaphylaxis

The group comprised 8295 patients aged 16 and above who sought treatment at the outpatient allergy clinic of Sivas Cumhuriyet University Faculty of Medicine, specifically within the Department of Chest Diseases, Division of Allergy and Clinical Immunology, during the period between July 2, 2018, and December 10, 2019. This retrospective analysis identified 77 cases (n=77) where adrenaline auto-injectors were prescribed and coded under the ICD-10 designation T78.2, indicating anaphylaxis. Our study revealed that the incidence of anaphylaxis among admissions to the allergy outpatient department was less than 1%, specifically amounting to 0.009%.

Demographics and characteristics of the patients with anaphylaxis

A total of 77 patients were included in the evaluation, with a mean age of 40.29 (13.77) years. Of these, 47 were female, and 30 were male. Among the patients, 73 (94%) had atopic diseases. Allergic diseases were categorized as single-type and multiple allergic diseases. Single-type allergic diseases comprised venom allergies (*Apis mellifera* and *Vespula vulgaris*) in 18 cases (23%), drug allergies in 11 cases (14%), food allergies in four cases, respiratory allergies in six cases, and cutaneous allergies in three cases. Multiple allergic diseases were identified in 31 patients (40%) (Figure 1). Among the 77 patients, 39 (51%) reported drug allergies, with predominant sensitizations to NSAIDs (43%) (Table 1).

A total of 32 individuals (41%) had a history of chronic illness,, 24 individuals (31%) reported chronic drug usage, with ten of them (12%) specifically using anti-hypertensive medications (Table 1).

Figure 1: Distribution of atopic diseases among patients with anaphylaxis (shown as number)

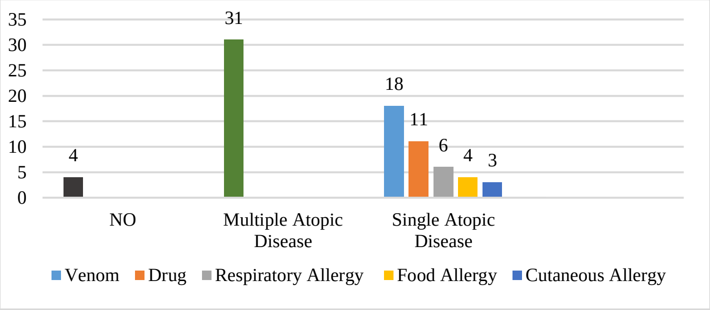


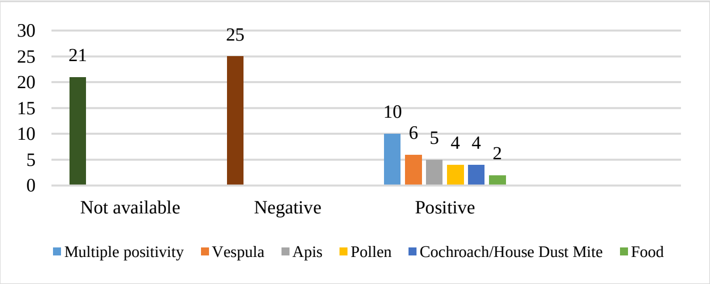
Table 1: General characteristics of patients with anaphylaxis.

Variables	Number, %
Total number of patients	77
Age, mean (SD) (years)	40.29 (13.77)
Gender (female/male)	47/30
Chronic disease	32 (41%)
Chronic drug usage	24 (31%)
Anti-hypertensive drug usage	10 (12%)
Atopic disease	73 (94%)
History of drug allergy	39 (51%)
History of Food Allergy	19 (24%)
Prick test results (+/-/not performed)	31 (40%) /25 (32%) /21 (27%)

SD: Standard deviation

Prick tests were administered to 56 patients (72%), of whom 25 individuals (44%) yielded negative results. Equally observed were sensitivities to pollen, cockroach, and house dust mites, each accounting for four cases. Polysensitization was evident in ten patients; only two exhibited positive food prick test responses. Interestingly, although cases of anaphylaxis stemming from *Apis mellifera* were more numerous than those from *Vespula vulgaris*, the instances of *Vespula vulgaris* reactivity exceeded those of *Apis mellifera* reactivity in prick tests (Figure 2). Regarding prick test positivity, venom accounted for 82% of anaphylactic cases, while for those with prick test negativity, drug allergies were the predominant cause (68.2%) (*P*=0.016). Notably, the presence of sensitivities to inhalant allergens and the presence of multiple allergen sensitivities did not significantly impact the etiology of anaphylaxis (*P*<0.001) (Figure 2).

Figure 2: Prick test results of the patients with anaphylaxis (shown as numbers)



Certain patterns emerge when assessing the relationship between the etiology of anaphylaxis and various atopic diseases, prick test results, and specific prick test outcomes. Notably, when neither drug nor venom allergy is present, anaphylaxis is solely attributed to food allergies (100%) (*P*<0.001). In cases where venom allergy is present, venom is identified as the predominant cause (95%), whereas in the absence of venom allergy, drug allergy assumes an 86% causal association (*P*<0.001).

Clinical characteristics of the anaphylaxis episodes

Based on a systematic assessment, cutaneous symptoms were observed in 94% of cases, respiratory symptoms in 88%, cardiovascular symptoms in 63%, neurological symptoms in 57%, and gastrointestinal symptoms in 12% of all patients.

Additionally, 55% of the patients experienced recurrent anaphylaxis episodes (Table 2).

Table 2: Clinical characteristics of anaphylaxis episodes

Variables	Number, %
Recurrent anaphylaxis	43 (55%)
Biphasic anaphylaxis	4 (5%)
Symptoms	
Mucocutaneous symptoms	73 (94%)
Respiratory tract symptoms	68 (88%)
Cardiovascular system symptoms	49 (63%)
Neurologic system symptoms	44 (57%)
Gastrointestinal tract symptoms	10 (12%)
Adrenalin administration	19 (25%)
Antihistaminic administration	77 (100%)
Corticosteroid administration	77 (100%)

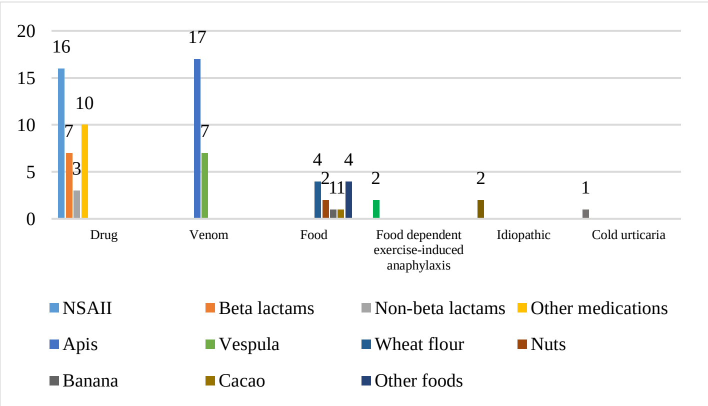
In cases of grade 4 anaphylaxis, cardiovascular and neurological symptoms were observed more frequently (100%) compared to other grades ($P<0.001$). Gastroenterological symptoms were also more prevalent in patients with grade 3 anaphylaxis compared to other grades ($P=0.002$). Furthermore, in situations where cutaneous symptoms were absent, grade 4 anaphylaxis was more prevalent (80%) than grade 2 anaphylaxis ($P=0.047$).

The causes of anaphylaxis included drugs (47%), venom (31%), food (16%), food-dependent exercise-induced reactions (n=2), idiopathic cases (n=2), and cold urticaria (n=1) (Figure 3). A gender-based comparison of anaphylaxis etiology revealed that drug- and food-related anaphylaxis was notably more frequent in women than men ($P=0.032$ and $P=0.042$, respectively). Regarding venom allergies, instances of anaphylaxis linked to *Apis mellifera* were significantly more prevalent than those related to Vespula ($P=0.028$) (Table 3).

Table 3: Etiologies of anaphylaxis according to the gender

Etiology	Female	Male	*P*-value
Drug	25	11	0.032
Food	8	4	0.042
Wheat flour	3	1	
Others	5	3	
Venom	12	12	>0.05
Apis mellifera	9	8	
Vespula vulgaris	3	4	
Idiopathic	1	1	>0.05
Food-dependent exercise-induced	0	2	

Figure 3: The triggers of anaphylaxis are categorized according to the etiologies (The frequencies are given as numbers).

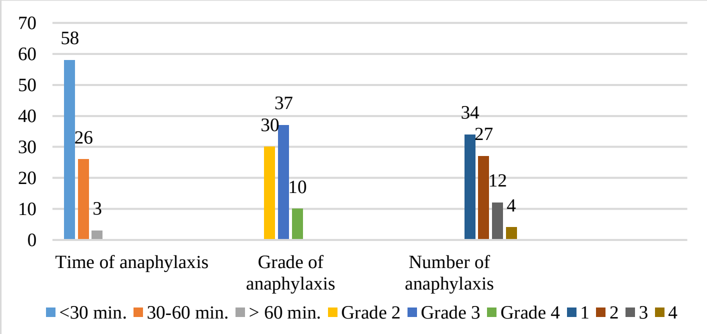


Both cases of food-dependent exercise-induced anaphylaxis were male, and the reaction occurred following mild exercise or even walking within the initial 10 min after eating. In both instances, skin tests yielded negative results. The diagnosis was established through patient history (anamnesis). Given that the suspected allergen could be wheat protein based on existing literature, the diagnosis was confirmed by implementing an elimination diet and restricting exercise for the initial 2 h after meals, leading to the disappearance of the symptoms.

In the emergency room, a patient with cold urticaria received an anaphylaxis diagnosis after presenting with widespread cutaneous manifestations, shortness of breath, palpitations, and dizziness following exposure to extremely cold temperatures during winter. Among instances of drug-related anaphylaxis, the predominant culprits were non-steroidal anti-inflammatory drugs (NSAIDs) (44%) and beta-lactams (10%). In food allergens, anaphylaxis was most frequently associated with wheat flour, although there were also cases triggered by bananas, cacao, and nuts (Figure 3).

Symptoms manifested within 30 min in 62% (n=58) of cases and within 1 h in 33% (n=26) of patients. Following the Mueller scale of anaphylaxis, 38% (n=30) experienced grade 2 reactions, 48% (n=37) had grade 3 reactions, and 12% exhibited grade 4 reactions (Figure 4).

Figure 4: The characteristics of the anaphylaxis episodes are categorized according to the time, grade, and number of the episodes (The frequencies are given as numbers).



Management of the anaphylaxis episodes

Merely 25% of cases received epinephrine injections upon arrival at the emergency department, with all individuals also being administered antihistamines and corticosteroids (Table 2).

It is important to note that, in our country, the acquisition of an adrenaline auto-injector necessitated a prescription from allergists; post-emergency service administration, the prescription of adrenaline auto-injector was not feasible.

Treatments and follow-up of the anaphylaxis patients

Venom immunotherapy was administered for cases with venom allergies. Oral provocation tests were conducted using alternative medications to identify safe options for those allergic to NSAIDs and antibiotics. Drug skin tests were not feasible due to challenging circumstances and inadequate facilities for patients with drug allergies. In cases of drug sensitivity, oral provocation was predominantly carried out using COX-2 inhibitors for those reacting to COX-1 inhibitors, and non-beta-lactam antibiotics were employed for individuals with beta-lactam antibiotic allergies.

Furthermore, comprehensive drug and food allergy cards were provided to patients, containing detailed information. Guidance was imparted on recognizing the significance of managing food allergies within their social lives. Precautions specific to cold urticaria were also communicated. Given that the city of Sivas, where our study is situated, experiences prolonged sub-zero temperatures during the winter as one of Turkey's coldest cities, individuals in these cases were advised to carry an adrenaline auto-injector. Notably, heightened vigilance was stressed in instances of cold urticaria due to the inherent risk of anaphylaxis in physical urticaria conditions. Every patient received instruction in the proper use and carriage of adrenaline auto-injectors.

Discussion

In our study, we conducted a retrospective analysis of anaphylaxis cases admitted to the allergy outpatient department of a tertiary university hospital in the northeast region of Turkey. We determined the frequency of anaphylaxis among patients seeking care at this single center. Our study revealed that anaphylaxis is exceedingly rare among admissions to the allergy outpatient clinic. According to existing literature, the lifetime prevalence of anaphylaxis ranges from 0.5% to 2% [9]. Research conducted in Korea demonstrated that anaphylaxis in adults rose from 8 to 13 cases per 100,000 individuals between 2007 and 2011 [10]. This upward trend in anaphylaxis incidence can be attributed to advancements in diagnostic methods and the increasing frequency of allergic diseases [11].

In a nationwide study conducted by Civelek et al. [12], a total of 843 cases were examined. The study revealed a predominance of females among anaphylaxis cases involving individuals older than 10 years, with venom identified as the primary etiological factor. In our study, drugs emerged as the leading cause of anaphylaxis within the general population. However, when analyzed by gender, drugs were the primary cause of anaphylaxis among women, whereas venom held the top position among men. Nearly 95% of the cases we investigated had a history of allergic disease. Conversely, drug allergies were frequently noted in the existing literature, particularly in cases of adult anaphylaxis, with up to 50% of cases displaying atopic tendencies [10,13,14].

Parallel to our findings, studies from China and Pakistan also identified drugs as prominent culprits in anaphylactic episodes [15,16]. The incidence of venom-induced anaphylaxis displayed significant variation across different populations, ranging from 1.5% to 59% [17]. In our country, venom-related anaphylaxis is particularly prevalent, a phenomenon attributed to the substantial number of individuals engaged in beekeeping and heightened awareness of the condition [18].

Food-induced anaphylaxis in adults is a rarity compared to children, with nuts/peanuts triggering the highest susceptibility, closely trailed by seafood sensitivity [19,20]. Within our study, wheat flour emerged as the leading cause of food sensitivity, although we also identified sensitivities to bananas, cacao, and nuts.

Literature data indicate a greater susceptibility to allergic diseases among female patients. This propensity is attributed to the augmenting role of estrogens in mast cell activation and allergen sensitization, whereas progesterone has been demonstrated to enhance sensitivity within target organs, exhibiting a synergistic impact. Consequently, this interplay leads to a prevailing female presence in non-venom-allergic conditions [21]. In the context of venom allergies, however, a male predominance persists. This phenomenon is primarily ascribed to the fact that men predominantly undertake beekeeping, resulting in a higher frequency of bee stings among the male population [17].

Typically, mucocutaneous manifestations are prevalent; however, cardiovascular and neurological symptoms occur more in grade 4 anaphylaxis cases. While dermatological manifestations are frequently documented in the literature and align with our findings, it’s imperative to recognize that anaphylactic reactions can manifest without skin involvement and even with cardiovascular collapse. In instances where skin involvement is lacking, diagnosing anaphylaxis becomes more challenging, resulting in a decrease in the administration of adrenaline when cardiovascular symptoms are present [22,23].

Collapse is less commonly observed in cases of food-related anaphylaxis, with gastrointestinal symptoms taking on a more anticipated role [24]. Conversely, in instances of venom and drug-induced anaphylaxis, cardiovascular symptoms are more likely and have been more frequently linked to fatal outcomes [18].

In a nationwide study, biphasic reactions were documented at 4.3%, while recurrent episodes of anaphylaxis were observed in 60% of cases [12]. In our study, a notable proportion – over 20% – experienced two episodes, and 30% had three separate anaphylactic episodes. Within our study, the incidence of biphasic anaphylactic reactions stood at 5%, recurrent cases were noted in 55%, and adrenalin administration was administered at a rate of 25%. Biphasic reactions frequently arise due to delayed or inadequate administration of adrenaline and are most commonly reported within the initial 8 h. As a standard protocol, individuals presenting with anaphylaxis should undergo at least 8 h of observation within emergency departments [25].

Similar to our own country’s experience, the rate of epinephrine prescription spans from 10% to 40%, and referral rates to allergy specialists fluctuate between 10% and 60%, as reported in the literature [26,27]. The prevention of biphasic and recurrent anaphylactic episodes hinges upon enhancing the awareness of healthcare providers regarding accurate diagnosis, effective treatment, and diligent follow-up. The endorsement of prescribing an adrenaline auto-injector holds significance, particularly in outdoor settings where venom allergies or food allergies are pertinent. Nevertheless, when a safe alternative exists for drug allergies, the prescription of an adrenaline auto-injector may not be deemed necessary.

Limitations

The principal limitation of our study resides in its limited sample size and retrospective design, coupled with the reliance on patient-reported data. Inherent to our retrospective approach is the potential for documentation bias, while recording patient-reported data introduces the possibility of data collection bias. Aspects such as the grading of anaphylactic reactions and determination of etiology were derived from the electronic patient files, introducing potential recall bias since they stem from patients’ recollections. To mitigate this bias, a consistent allergist oversaw each patient and posed standardized inquiries, with the resultant data meticulously entered into the hospital’s electronic records system. Notably, a paramount limitation influencing epidemiological data stems from the tendency in our country, akin to global trends, for physicians, patients, and/or caregivers to delay the diagnosis of anaphylaxis unless unmistakable shock-related indicators are evident or, in some instances, not making the diagnosis at all. In such scenarios, accurate diagnosis remains elusive, and the referral to an allergist becomes unattainable.

Anaphylactic cases triggered by drugs were managed by implementing alternative drug recommendations. This approach is adopted due to physicians' inclination to opt for safe alternative drugs when circumstances for conducting skin tests are not conducive – factors like the absence of secure test sites, time constraints, challenges in describing the suspected drug, or patient use of medications affecting the testing process, among others. Regrettably, diagnostic tests for confirmation or drug provocations to pinpoint the causative drug could not be administered. It's worth noting that provocation tests stand as the benchmark for diagnosing genuine drug allergies and should be conducted under safe conditions. Regarding non-drug origins, standardized allergen extracts were employed for skin prick tests; however, no provocations involving venom or food sources could be conducted.

In addition, basal tryptase could not be measured because laboratory conditions were not possible. An increase of tryptase [(1.2 × baseline tryptase) +2 µg/L)] measured in serum within the first 2 h after the anaphylaxis attack supports the diagnosis [28].

Systemic mastocytosis and mast cell activation syndromes, entities encompassed within the anaphylaxis differential diagnosis, underscore the utility of basal tryptase levels. When evaluating patients' medical history, factors prompting physicians to consider mast cell disorders encompass the recurrence of numerous anaphylactic episodes, instances of idiopathic or grade 4 anaphylaxis, the emergence of direct cardiovascular manifestations devoid of cutaneous signs, and anaphylactic reactions linked with venom allergies [29].

Nevertheless, it is crucial to recognize that tryptase is not exclusively indicative of anaphylaxis. Particularly in instances of mast cell disorders or hereditary alpha tryptazemia, both susceptibility to anaphylaxis and heightened basal tryptase levels (normal basal tryptase <11.5 ng/ml) can manifest. Consequently, when anaphylaxis is suspected, basal tryptase measurements should be taken at least 24 h after induced tryptase measurements. It's important to note that tryptase levels may not consistently rise in children, particularly in anaphylactic episodes characterized by food-related reactions, especially those presenting with gastrointestinal symptoms. In summary, the absence of an elevated tryptase level during an anaphylactic event does not definitively rule out the occurrence of anaphylaxis [30,31].

Strengths

Literature reviews have predominantly centered on subgroups of anaphylaxis, conducting subgroup analyses that delve into triggers such as drugs or food. While epidemiological studies on anaphylaxis are within the literature, our country's landscape lacks investigations that ascertain the risk associated with anaphylactic incidents [32]. In the current study, we aimed to ascertain the prevalence and distribution of anaphylaxis triggers across all cases attending a solitary allergy outpatient clinic, thereby illuminating the region's epidemiological insights.

Future research

There is a paramount need to educate healthcare providers during their post-graduate training about the diagnosis and treatment protocols for anaphylaxis, ensuring that these essential teachings are reiterated through mandatory annual training sessions. Employing technological reminders such as mobile phones, smart watches, and virtual intelligence systems can effectively enhance early awareness of anaphylactic risks. In laboratory settings, blood samples should be collected under optimal conditions for accurate tryptase measurement to support diagnostic endeavors. The serum must be segregated and appropriately stored if an immediate analysis is unfeasible. Patients should be strongly encouraged to carry a minimum of two auto-injectors, equipping them to recognize anaphylactic symptoms and self-administer them as needed. Organizing group activities –in-person or online – with patients can aid in dispelling misconceptions such as needle apprehensions and concerns regarding adrenaline's side effects.

Strategic social responsibility initiatives, particularly within educational institutions and workplaces, are essential for fostering awareness about triggers such as food allergies and anaphylaxis. These initiatives should emphasize first-response training to equip individuals with the necessary skills to handle anaphylactic emergencies effectively [2].

Conclusions

Our study presents the inaugural dataset for analyzing the northeastern region of Turkey. Within the scope of anaphylaxis studies in our country, there has been a notable absence of research into the outcomes of adult cases within this specific region, particularly through the eyes of allergist evaluation.

While allergic diseases tend to exhibit a higher prevalence among females, our anaphylaxis study yielded comparable frequencies between the female and male genders. The prominence of venom allergy as the second leading cause of anaphylaxis etiology, coupled with the observation that nearly all venom-induced allergies occurred in males engaged in beekeeping, appears to have influenced this gender-based distribution. Our findings underscore the enduring prominence of drug-induced anaphylaxis as the primary etiological factor – a preventable trigger that remains at the forefront. Notably, the incidence of recurrent anaphylaxis stood alarmingly high at 55%, shedding light on the insufficient awareness surrounding this matter, particularly in cases where triggers such as drugs and food could be averted with greater knowledge. The recurrent exposure to the same triggers emphasizes the need for heightened understanding. Implementing immediate adrenaline administration is a pivotal preventive measure against biphasic and prolonged anaphylactic episodes. Strikingly, our investigation reveals a concerning statistic: only 25% of anaphylaxis cases in our region receive adrenaline promptly.

NSAIDs and antibiotics stand out as the prevailing culprits in etiology. This observation underscores the imperative for all medical practitioners, pharmacists, and healthcare units to comprehensively understand anaphylactic triggers. By doing so, these stakeholders can effectively heighten vigilance when providing outpatient and inpatient care, including surgical procedures. Furthermore, a compelling need exists to foster patient awareness concerning drug-induced anaphylaxis – a preventable catalyst in this context.

Sivas, the focal point of our study, assumes a significant role in our nation as a hub for beekeeping and honey production. Despite venom sensitivity emerging as the foremost solitary allergic condition among our admitted patients, it assumes the second position in the hierarchy of anaphylaxis etiology. It remains common knowledge that Venom Immunotherapy (VIT), a treatment regimen extended to our venom-allergic cases, is the exclusive therapeutic approach capable of altering the trajectory of this ailment. Encouragingly, VIT demonstrates both efficacy and safety right from its initial administration.

Furthermore, an exhaustive patient history becomes imperative in instances of anaphylaxis incited by food-dependent exercise – a notably rare yet acknowledged category of anaphylaxis. While these cases remain symptom-free when physical exertion remains below a certain threshold after consuming food, symptoms manifest when exercise coincides with food ingestion. The intricacies of this presentation often render differential diagnosis challenging, even for allergy specialists. Once accurately diagnosed, proactive measures and medical interventions effectively manage the condition, greatly enhancing the affected individuals' quality of life.

Adrenaline administration presents no contraindications when faced with an anaphylactic episode and should be promptly administered without reservation. Within the purview of our study, the intended recipients of this guidance encompass a diverse group of medical practitioners. Among them are clinical allergists, spanning specialists and sub-specialists, and primary care physicians, internists, emergency physicians, anesthesiologists, and intensive care specialists. This directive also extends to nurses, dietitians, and other healthcare professionals. Essential to effective management, the ability to differentially diagnose anaphylaxis falls within the domain of emergency room physicians. In such cases, a swift and accurate diagnostic discernment, based on history and physical examination findings aligning with anaphylaxis, warrants the immediate administration of adrenaline.

In conclusion, our study is noteworthy due to the infrequency of anaphylactic occurrences among cases attending the tertiary allergy immunology outpatient clinic in the northeastern region of Turkey.

Notwithstanding its limitations, our study fills a crucial gap by furnishing insights into a region hitherto unexplored, emphasizing anaphylaxis – a matter of significance for practitioners across various medical disciplines and healthcare sectors. The implications of our findings underscore the essentiality of bolstering awareness surrounding the diagnosis and management of anaphylaxis in both emergency and primary healthcare settings, both prior to and after graduation.

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