

The Incidence and Frequency of Various Causes of Angioedema in Emergency Medicine

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Objective. Angioedema (AE) is a potentially life-threatening event. We investigated the etiology of AE, with the emphasis on bradykinin-induced angioedema treatment in emergency medicine. **Methods.** The retrospective study included 237 patients with AE, who were examined and treated in two hospitals (group A and B) in Croatia from 2009 to 2016. The location and duration of AE, data about chronic diseases and treatment, potential causative agents (food, drugs, insect bites and chemicals), physical examination data and the subsequent treatment were analyzed. **Results.** There was no statistical difference regarding age or comorbidities but there was a statistically significant difference in etiology between the groups (Chi-square, $P=0.03$). Renin-angiotensin-aldosterone system (RAAS) blocker induced AE was the main cause of emergency attendance in group A (37.5%) and among the leading causes in group B (18.8%). Bradykinin-induced AE (hereditary angioedema (HAE) and RAAS-AE) were the leading causes in a total of 75 (31.5%) patients. RAAS-AE was treated with glucocorticoids and antihistamines. HAE attacks in both groups (2/7 patients, 1.5/6%) were treated with specific therapy. Other causes of AE in groups A/B were insect bites (15/23 patients, 13.5/20%), use of antibiotics/analgetics (11/17 patients, 9/15%), gastroesophageal reflux disease (10/11 patients, 8/9%), neoplasms (5/6 patients, 4/5%) and idiopathic (32/31 patients, 26.5/26%). 21% of patients were hospitalized. **Conclusion.** Bradykinin-mediated AE was the main cause of emergency attendance associated with AE. Advances in the treatment of HAE, with case reports of patients with RAAS-AE treated with C1 esterase inhibitor concentrate or bradykinin receptor antagonist, may prove to be a new, reliable and efficacious therapy option.

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Received: 29 December 2017

Accepted: 4 May 2018

Key words: Angioedema ■ Emergency ■ Bradykinin ■ Icatibant ■ Plasma-derived C1-inhibitor.

Introduction

Quinckes edema or angioedema (AE) is an transient, localized swelling of the deep dermis or subcutaneous/submucosal tissues (1). Angioedema usually manifests in the upper airway, and the head and neck region (1, 2). Histamine and bradykinin are two main mediators involved in AE occurrence,

inducing endothelial cell permeability (3-7). Histamine-mediated AE with recognizable triggers, such as an insect bite, food, medication, and rapid onset of swelling, are often accompanied by urticaria and itching (3). Bradykinin-induced angioedema, including hereditary (hereditary angioedema (HAE) types I (due to low level of C1 ester-

ase inhibitor (C1 INH)) and II (dysfunctional C1 INH), or HAE with normal C1 INH) or nonhereditary forms (nonallergic angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) induced angioedema and acquired AE due to C1 INH deficiency) with a history of recurrent swelling and abdominal pain, are not associated with urticaria (3, 8, 9). Differentiation is essential for treatment planning since bradykinin mediated angioedema does not respond to conventional antihistamine and corticosteroid therapies (8). Angioedema due to exposure to external agents (insect bites, food, environmental allergens) is very common. Including gastroesophageal reflux disease (GERD), it is usually identified by the patients themselves (10). The role of GERD in the development of angioedema is still controversial, especially in children (10, 11). Some tumors may produce biogenic amines, such as histamine, and release them into the circulation causing angioedema (12). Acquired AE with low C1-INH is connected with autoimmunity or malignant lymphoproliferative disorders (13).

Drugs may induce AE by three mechanisms: an allergic IgE-mediated reaction accompanied by urticaria (such as beta-lactam antibiotics); non-allergic, such as AE induced by aspirin and nonsteroidal anti-inflammatory drugs (NSAID); and the most frequent (10-25% of all cases, never associated with urticaria) including inhibition of bradykinin degradation, induced by renin-angiotensin-aldosterone system (RAAS) blockers, such as ACEI or ARBs (10, 14, 15). The RAAS plays an important role in the regulation of kidney blood flow and blood pressure, with the emphasis on angiotensinogen, which is changed from angiotensin I to angiotensin II by the angiotensin I-converting enzyme (ACE) (known as kininase II). Angiotensin II is a key factor for the inactivation of bradykinin which originates

from the degradation of kininogen by kallikreins. The metabolism of bradykinin does not depend only on ACE. Several other enzymes are involved and a deficiency of any of these enzymes (due to a genetic polymorphism) will increase the risk of developing AE (15-18). This has been observed in black and Hispanic races (6, 15, 19, 20). AE with ACEI therapy (ACEI-AE) is more frequent than for other RAAS blockers, and is between 0.1% and 2.2% (6). The development of edema in the upper respiratory tract is unpredictable. The management of ACEI-AE begins by ceasing administration of ACEI as the suspected drug (6, 21). It is important to tell the patient not to take any RAAS drugs ever again, such as ARBs, while 4% of patients who have had ACEI-AE will develop AE when they switch to ARBs (22). The literature suggests that some other drugs that inhibit the mammalian target of rapamycin (mTOR inhibitors), if taken with ACEI, affect the incidence of ACEI-AE (23). There is no approved treatment for this potentially life-threatening situation (22, 24). As Craig et al. reported, specific drugs, such as a C1-INH concentrate and bradykinin B2 receptor blocker icatibant, which have been approved for acute attacks of HAE type 1 or 2, successfully resolved attacks of different types of bradykinin-induced AE (8, 25, 26).

The goal of this study was to determine the incidence of AE, and whether there is a difference in the causes and frequency of AE as a major reason for emergency attendance, with special emphasis on bradykinin-induced angioedema frequency and treatment.

Materials and methods

A retrospective, two-center analysis was conducted of all patients with AE found in the Emergency Units' medical databases. The study included a total of 237 patients with AE who were examined in the Emer-

gency Units of two hospitals in Croatia: Merkur Clinical Hospital, Zagreb (120 patients in group A) and the Department of Otorhinolaryngology, Šibenik General Hospital, Šibenik (117 patients in group B) from January 2009 to January 2016. Anamnestic findings (location and duration of AE), data about chronic diseases, treatment (primarily exposure to ACEI, ARBs) and potentially causative agents (food, drugs, insect bites and chemicals) along with the physical examination data and subsequent treatment, were analyzed for each patient with AE. As Zingale et al. proposed, ACEI-AE was diagnosed when angioedema was repeatedly present during ACEI therapy and ended upon withdrawal of the medication (10).

Since there is still no standardized severity scoring system for AE, we graduated AE as grade 0= no local reaction; grade 1= mild (isolated local reaction of the skin or mucosa); grade 2= intermediate (involves more distant skin; upper airway); grade 3= severe (potentially life-threatening condition manifesting with laryngeal symptoms); grade 4= severe multi-system reaction. A composite score was calculated using the visual analog scale, with intensity ranging from 0 to 10 (higher scores indicating more severe symptoms), using the average of the measurements for the six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, feeling of pressure) as proposed by Bas (7).

Statistical analysis

Data were described using descriptive statistical methods. Differences in categorical variables were tested with the Chi-square test. The normality of the distribution of numerical variables was tested by Shapiro-Wilk's test. All P values were two-sided. The level of significance was set at Alpha =0.05. The statistical analysis was performed using STATISTICA 13.1.

Results

The median age in groups A and B was 51.7 years, with 50.5% males (Table 1). The graduation of AE in this study was generally mild, characterized by mean severity scores of 1 or 2 (20%) on a scale of 0 to 4. The mean composite score on a visual-analogue scale of 0 to 10 was approximately 3.

The etiology of AE is shown in Table 1. Bradykinin-induced AE (ACEI/ARB and HAE) was the leading known cause of AE in the investigated group, in a total of 75 (31.5%) patients. AE caused by ACEI/ARB blockers was present in 67 (28%) patients. Patients with ACEI-AE were older and there were more females represented (70.5% female; mean age, 63.4 ± 11.5 years) when compared to all AE patients. The locations of AE included swelling of the face and lips (48.1% of patients), tongue (37.5%), larynx (12.5%) and upper airways (2.9%). The duration of exposure to ACEI was between 1 and 721 days with a median of 452 days. Duration of AE symptoms was from 2 to 5 days. All patients with ACEI-AE had normal C1-inhibitor levels. There was no statistically significant difference regarding age or comorbidities (hypertension, diabetes, heart failure, kidney disease) but there was a statistically significant difference in etiology between the groups (Chi-square, $P=0.03$). All the patients were under the appropriate therapy for comorbidities. In group A the patients used drugs in their chronic therapy more than in group B (such as diuretics in fixed combination with ACEI, such as ramipril in 80%). All investigated patients with symptoms of AE, except HAE patients (3.8%), were treated with antihistamines, corticosteroids and epinephrine if needed (Table 1.).

Twenty-one patients (8.9%) diagnosed with GERB were also treated with proton pump inhibitors (PPI) intravenously. Fresh frozen plasma was administered success-

Table 1. Demographic and clinical characteristics of patients with angioedema

| Characteristics | Group A | Group B | Treatment | Total | P* |
|-------------------------|------------------|------------------|--------------------|------------------|------|
| Gender (N; %) | | | | | |
| Male | 62 (51.7) | 60 (51.3) | - | 122 (51.5) | |
| Female | 58 (48.3) | 57 (48.7) | - | | 0.95 |
| Age (Year, Median, IQR) | 52.1 (41.8 – 63) | 50.8 (40.2 – 65) | - | 51.7 (40 – 60) | 0.34 |
| Etiology (N; %) | | | | | |
| ACEI/ARB | 45 (37.5) | 22 (18.8) | A+C | 67 (28.3) | |
| Idiopathic | 32 (26.5) | 31 (26.5) | 98.4% A+C 1.6% FFP | 63 (26.6) | |
| Insect bite | 15 (13.5) | 23 (19.7) | A+C | 38 (16) | |
| Antibiotics; NSAID; OTC | 11 (9) | 17 (14.5) | A+C | 28 (11.8) | 0.03 |
| GERD | 10 (8) | 11 (9.4) | A+C+PPI | 21 (8.9) | |
| Neoplasms | 5 (4) | 6 (5.1) | A+C | 11 (4.6) | |
| HAE | 2 (1.5) | 7 (6) | specific | 9 (3.8) | |
| Total (n) | 120 (100) | 117 (100) | | 237 (100) | |

*Chi-square test; IQR=interquartile range; ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; NSAID=NonSteroidal anti-inflammatory drugs; GERD=Gastroesophageal reflux disease; HAE=Hereditary angioedema; N=Number of patients; A+C=Antihistamines+corticosteroids; FFP=Fresh frozen plasma; PPI=Proton pump inhibitor; OTC=Over the counter.

fully in only one patient in group A, when standard therapy failed. HAE patients were hospitalized for specific therapy, such as C1-INH concentrate (plasma derived or recombinant) or icatibant. In all patients presenting with mild AE (the majority of the population), monitoring in hospital for at least 6 h was advised. Patients with clinically significant obstruction of the upper airway (21%) were hospitalized in the intensive care unit or the Department of Otorhinolaryngology for a few days. There was no need for tracheostomy in any patient with ACEI-AE in either group. Tracheostomy was a life-saving treatment for one patient in group B with HAE.

Discussion

Recent studies have revealed AE as the most frequent and increasing disorder that results in hospitalization (14). In comparison with the study by Loftus et al., twice as many patients (21%) needed to be hospitalized for severe angioedema in our investigation (15). In 26.5% patients in group B the cause of AE

was unidentified, which makes differential diagnosis and management even more challenging, especially in general hospitals with limited diagnostic and therapeutic tools. The role of GERD or Helicobacter pylori infection in AE remains unclear. Recent studies have presented the opposite results of AE resolution connected with eradication of Helicobacter pylori (10, 27-29). Patients indicating GERD angioedema etiology in this study (8.9%) were treated additionally with PPI. This is the first study in Croatia to analyze the frequency and treatment of bradykinin-induced angioedema as a major cause of emergency attendance. This investigation showed an etiological statistically significant difference between the groups (Chi-square, P=0.03) but the same therapeutic pattern in both clinical and general hospital centers. 20–45% of the patients admitted to the emergency rooms for suspicion of AE are suffering from an AE mediated by bradykinin (6, 15). However, reliable tests that can differentiate bradykinin angioedema from angioedema due to other causes are still not routinely available. In recent years,

the growth of the use of RAAS blockers has resulted in an increased prevalence of angioedema. The causes of AE listed in Table 1 show that ACEI/ARB was the main cause of emergency attendance in group A (37.5%) and among the leading causes in group B (18.8%). It occurs very often in patients who use several drugs for chronic therapy, such as diuretics (as in group A), accentuating the burden of ACEI among the at-risk population, especially in female patients, with well-known higher prevalence noticed in 70.5% females in our investigation. AE is characterized by a local, transient, asymmetrical, sudden and painful swelling of the subcutaneous (facial) and submucosal (oropharyngeal and laryngeal) tissues that occasionally requires tracheostomy as a life-saving treatment, as it did in one patient with HAE in our study (6). If ACEI is the unrecognized cause of angioedema, it relapses with ACEI therapy, as was the case in this study. The drugs commonly used to treat histamine-induced AE of allergic origin (glucocorticoids, antihistamines, epinephrine) are ineffective against bradykinin-induced AE (3, 6). In the investigated groups, ACEI-AE angioedema persisted for 2-4 days with poor resolution using these therapeutics. That emphasizes the need for new therapeutic solutions, especially when the patient's airway is compromised. Specific medications (plasma derived or recombinant C1-INH concentrate, icatibant) for HAE or acquired AE might be the treatment of choice, as has been demonstrated in numerous studies (21, 30-33).

There is a lack of studies using large cohorts of patients with ACEI-AE. The patients with ACEI-AE included in this study were not treated with C1-INH concentrate or icatibant, although in one patient with severe AE of the tongue, poor resolution of AE was noticed. However, the recent studies by Straka and Sinert et al. do not support the efficacy of a bradykinin B2 receptor antagonist in ACEI-AE (34, 35). Fresh frozen

plasma that contains natural ACE and C1-INH effectively treats ACEI-AE, and was successfully applied in one patient with an unknown cause of AE (6). Plasma derived or recombinant C1-INH concentrate and icatibant were successfully administered during HAE attacks in all the investigated patients (3.8%) in groups A and B (36).

Conclusion

AE resulting from bradykinin-induced AE (ACEI/ARB and HAE) was the main cause of emergency attendance of patients. Identifying the cause and withdrawal of ACEI is key to management. Mild cases of ACEI-AE may respond to antihistamine or corticosteroid therapy, but moderate to severe cases do not. Advances in the treatment of HAE and case reports of patients with ACEI-AE treated with C1-INH concentrate or bradykinin receptor antagonist show that they may be a safe and efficacious therapeutic option for AE.

What is already known on this topic

Angioedema (AE) is a transient, localized swelling usually manifested in the upper airway, causing potentially life-threatening swelling of the mouth and throat. The most frequent mechanism of AE induced by drugs (10-25% of all cases, never associated with urticaria) includes inhibition of bradykinin degradation, induced by the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. There is no approved treatment for this potentially life-threatening situation.

What this study adds

This is the first study in Croatia analyzing the frequency and treatment of bradykinin-induced angioedema as a cause of emergency attendance. Bradykinin-induced AE was the leading cause in the investigated group in a total of 75 (31.5%) patients. Our study confirmed the poor response to glucocorticoid, antihistamine and epinephrine treatment in severe AE, and the need for new therapeutic options to improve resolution of AE.

Authors' contributions: Conception and design: LjKL and IP; Acquisition, analysis and interpretation of data: LjKL, TP and JJZ; Drafting the article: LjKL and IP; Revising it critically for important intellectual content IP, PP and SD; Approved final version of the manuscript: LjKL, TP, PP, JJZ, SD, IP.

Conflict of interest: The authors declare that they have no conflict of interest.

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