

Angioedema: A Review of 367 Episodes Presenting to Three Tertiary Care Hospitals

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Objectives: We evaluated the clinical characteristics of patients treated for angioedema, and determined the factors associated with the clinical course.

Methods: We performed a chart review of 367 episodes presenting from 1997 through 2008.

Results: The mean ($\pm$ SD) age was 51.8 ± 20.1 years; 65.7% of the episodes occurred in female patients; 62.4% of the episodes were in African American patients. The patients were on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for 49.1% of the episodes, and an inciting factor (diet change, minor trauma, or exposure to fumes) was present for 21.5%. We found that 75.7% of the episodes were type 1 angioedema, 5.7% were type 2, 1.4% were type 3, and 17.2% involved multiple sites; 58% of the episodes required admission. For 3.3% of the episodes, the patients were intubated, and in 0.3% of the episodes, the patients required a tracheostomy. Logistic regression identified non-African American race, allergies, alcohol use, use of ACE inhibitors or ARBs, multiple sites, and age as associated with the need for admission. Bivariate analysis identified age, multiple affected sites, stridor, hoarseness, dysphagia, and drooling as associated with intubation or tracheostomy.

Conclusions: The novel findings of this study are lower rates of airway intervention than reported previously and the fact that multiple affected sites were associated with admission and intubation or tracheostomy, particularly when the edema involved the larynx or hypopharynx.

Key Words: airway obstruction, angioedema, angiotensin-converting enzyme inhibitor.

INTRODUCTION

Angioedema, or angioneurotic edema, is characterized by painless, well-circumscribed areas of edema of mucosal or cutaneous surfaces. These usually nonpruritic, nonpitting areas may involve any part of the body, including the gastrointestinal tract, but they show a predilection for the upper aerodigestive tract. Angioedema involves the deep dermis and submucosal or subcutaneous levels, whereas urticaria is more superficial. Angioedema can be one of multiple components of anaphylaxis, which may also include urticaria, hypotension, and bronchoconstriction.

Angioedema is a relatively common diagnosis and has been reported to affect 10% of Americans during their lifetime.^{1,2} A female predominance has been reported in most studies.³⁻⁶ It is particularly common in African Americans.^{5,7-11} An increase in hospitalizations for angioedema has been reported in New York State since 1990.⁷ Of interest to otolaryngologists, the principal cause of morbidity and

mortality in patients with angioedema is airway compromise. Previous studies have found that patients with laryngeal and oropharyngeal angioedema are more likely to be admitted and to require airway intervention.^{3,6,12-14}

Angioedema is caused by increased vascular permeability with extravasation of fluid into the submucosal or subcutaneous tissues. The exact mechanisms differ among its causes, which include defects in C1 esterase inhibitor (hereditary and acquired angioedema), accumulation of bradykinin (angiotensin-converting enzyme [ACE] inhibitor-induced angioedema), and mast cell degranulation (immunoglobulin E-mediated immediate hypersensitivity). Hereditary angioedema occurs in the general population at a rate of 1 per 50,000, whereas acquired angioedema is rare. The most common causative agents resulting in angioedema are ACE inhibitors. The incidence of angioedema in patients treated with ACE inhibitors is between 0.1% and 2.2%.⁸ Studies have found that African-Americans are 3 times as likely to have ACE inhibitor-induced

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angioedema.¹¹ ACE inhibitor-induced angioedema has also been found to be a more clinically severe form and has more frequently required intensive care unit monitoring in some studies.^{13,15} Adverse reactions to other medications, foods, insect bites, minor trauma, and physical irritation have also been shown to produce angioedema.

Our initial objective was to determine whether the number of hospital visits for angioedema had been increasing over an 11-year study period and to evaluate trends in presentation and management. Because of the unexpectedly large number of angioedema visits identified by computer search and the small number of charts retrieved by the medical records departments, we were unable to fulfill this objective. Our study instead provides a retrospective chart review describing the inciting factors, presentation, and clinical course of patients with angioedema presenting to our urban, tertiary care institutions. In particular, we investigated factors associated with the need for admission and the need for airway intervention.

METHODS

Patient charts with a primary or secondary diagnosis of angioedema over the period between January 1, 1997, and May 1, 2008, at 3 tertiary care hospital centers in Brooklyn, New York (Long Island College Hospital, Kings County Hospital Center, University Hospital of Brooklyn) were requested for review. The review was approved by the Institutional Review Boards at all 3 institutions. The chart selection was conducted according to the International Classification of Diseases, ninth version (ICD-9) code 995.1 (angioedema).

The following information was extracted from the charts: sex, age, race, presenting history, medical history, prescribed medications, allergies, social history, change in diet, exposure to fumes, insect bites or trauma in the preceding 48 hours, known diagnosis of hereditary angioedema, history of angioedema, presenting symptoms, type of angioedema, need for admission, length of stay, need for intubation or tracheostomy, medical treatment, medication changes, results of immunologic workup if obtained, and outcome. The ethnic and racial composition of the neighborhoods of Long Island College Hospital and of the Kings County Hospital Center and University Hospital of Brooklyn was obtained from the United Hospital Fund-defined neighborhoods of the 2000 US Census.¹⁶

The presenting angioedema was classified into different types depending on location on physical examination according to a modification of the classification scheme described by Chiu et al.¹² Type 1

was defined as involving the face, lips, or oral cavity, including the oral tongue. Type 2 involved the soft palate and uvula, the base of the tongue, or oropharyngeal edema. Type 3 involved the larynx or hypopharynx. Although the classification of Chiu et al.¹² implied a progression, as none of his patients had isolated glottal or supraglottic involvement without oropharyngeal involvement, other authors have not reported such a progression.^{3,14} We classified our patients using the anatomic sites defined by Chiu et al.¹² and categorized the edema as involving multiple sites if more than one type was found.

Our initial intent was to determine whether the number of hospital visits for angioedema had been increasing over the 11-year study period and to evaluate trends in presentation and management. More than 3,000 records of angioedema visits were initially identified, and it was beyond the scope of the study to review every one. In addition, the manner in which the medical records departments were organized and the charts were stored at each hospital did not allow for a consecutive sample. Rather, the charts that were reviewed were the ones that were available electronically and easily accessible at the storage facilities. A total of 3,104 patient charts with a diagnosis of angioedema were initially identified by computer search (1,912 from Kings County Hospital Center, 911 from Long Island College Hospital, and 281 from the University Hospital of Brooklyn). A convenience sample of 387 charts was analyzed. Cases that were misdiagnosed or did not involve angioedema of the head and neck on physical examination were excluded. Incomplete charts or charts with missing information were also excluded. In the final study, 367 episodes of angioedema for 337 patients were included. We included 171 of the 1,912 charts (8.9%) from Kings County Hospital Center, 182 of the 911 charts (20.0%) from Long Island College Hospital, and 14 of the 281 charts (5.0%) from the University Hospital of Brooklyn.

Bivariate analysis using χ^2 or Fisher's exact test for categorical outcomes and 2-tailed *t*-tests for continuous outcomes was performed. Potential predictors of the need for admission on the bivariate analyses were entered into a logistic model by use of a backward elimination process. An a priori logistic regression model was also developed to evaluate factors thought to be most predictive of the need for admission in order to validate the model obtained from variables considered from the unadjusted analysis. SPSS version 17.0 (SPSS Inc, Chicago, Illinois) or Statistical Analysis Software version 9.2 (SAS Institute, Inc, Cary, North Carolina) was used for all analyses. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Over the 11-year period, 367 episodes of angioedema involving 337 patients were reviewed. The majority of visits (74%) occurred between 2005 and 2008, although at least some patients were treated during most years at all 3 hospitals. Of these patients, 314 had a single episode of angioedema, 19 had 2 episodes, 3 had 3 episodes, and 1 patient had 6 episodes. There was a female predominance, as 241 episodes (65.7%) occurred in women. The mean ($\pm$ SD) age at presentation was 51.8 ± 20.1 years (range, 9 months to 92 years). The ethnic and racial composition was 40 Caucasian (10.9%), 229 African American (62.4%), 54 Hispanic (14.7%), 9 other (2.5%), and 35 unknown (9.5%). At Long Island College Hospital, significantly more episodes occurred in African Americans as compared to non-African Americans than would be expected from the neighborhood ethnic and racial composition ($\chi^2 = 149.7$; $p < 0.0001$). Although 80.1% of the episodes at Kings County Hospital and SUNY Downstate occurred in African Americans, the difference was not statistically significant ($\chi^2 = 1.41$; $p = 0.234$). A history of angioedema was found for 108 episodes (29.4%), and no patient had a previous diagnosis of hereditary angioedema.

On presentation, patients were on ACE inhibitors for 168 episodes (45.8%), angiotensin receptor blockers (ARBs) for 7 (1.9%), and both ACE inhibitors and ARBs for 5 (1.4%). The duration of ACE inhibitor or ARB therapy was recorded for 20 episodes and ranged from several hours to 10 years. Two patients had a repeat episode caused by failure to discontinue their ACE inhibitors after a previous episode. Only 1 patient who had been on an ACE inhibitor was changed to an ARB because of a prior episode of angioedema. African Americans were significantly more likely to have ACE inhibitor or ARB-related angioedema than were non-African Americans (odds ratio, 2.03; 95% confidence interval, 1.26 to 3.28; $p = 0.004$). A few additional medications were also thought to trigger the angioedema, and overall, 190 of the episodes (51.8%) were assumed to be medication-related.

Possible inciting factors, other than a medication, occurring in the 48 hours before presentation were reported for 79 of the episodes (21.5%): a change in diet for 60 (16.3%), exposure to fumes for 6 (1.6%), insect bites for 11 (3.0%); and minor trauma for 2 (0.5%). Twenty-six episodes (7.1%) had multiple potential causes, and 123 episodes (33.5%) were idiopathic and not associated with an inciting event or a medication. Non-African American patients were more likely to have idiopathic angioedema than were

TABLE 1. BIVARIATE ANALYSIS PERFORMED WITH CHI-SQUARE OR FISHER'S EXACT TEST FOR CATEGORICAL VARIABLES ASSOCIATED WITH NEED FOR HOSPITAL ADMISSION

Variable	n	OR	95% CI	χ^2	p
Female	367	1.17	0.76 to 1.81	0.49	0.505
Non-African American	332	1.96	1.20 to 3.20	7.41	0.008*
Allergies	367	2.19	1.39 to 3.46	11.56	0.001*
Smoking	319	4.90	2.46 to 9.78	23.15	<0.001*
Alcohol	319	3.59	1.73 to 7.45	12.89	<0.001*
History of angioedema	367	1.34	0.84 to 2.12	1.52	0.246
ACE or ARB	367	2.81	1.83 to 4.33	22.73	<0.001*
Multiple admissions	158	11.63	1.50 to 90.41	8.40	0.003*
Stridor	364	2.22	0.23 to 21.52	0.50	0.641
Hoarseness	337	3.93	2.15 to 7.18	21.69	<0.001*
Dyspnea	359	1.90	1.01 to 3.56	4.10	0.051
Dysphagia	310	2.97	1.62 to 5.43	13.09	<0.001*
Rash	365	0.86	0.48 to 1.52	0.28	0.657
Drooling	297	6.04	1.33 to 27.5	6.88	0.012*
Multiple sites	367	5.47	2.61 to 11.48	23.92	<0.001*

For age (continuous variable), n was 367, mean difference was 12.45, 95% CI was 8.32 to 16.59, t (2-tailed) was 5.93, and p was <0.001 (statistically significant).

OR — odds ratio; CI — confidence interval; ACE — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker.

*Statistically significant at $\alpha = 0.05$.

African American patients (45.6% versus 29.7%).

The presenting symptoms were hoarseness or difficulty speaking for 77 episodes (21.0%), dysphagia for 67 (18.3%), dyspnea for 53 (14.4%), rash for 55 (15.0%), drooling for 14 (3.8%), and stridor for 4 (1.1%). Eighteen episodes (4.9%) involved non-head and neck (extremity) swelling, and 10 episodes (2.7%) had abdominal symptoms suggestive of possible bowel edema. Isolated type 1 angioedema was found for 278 episodes (75.7%), isolated type 2 for 21 episodes (5.7%), and isolated type 3 for 5 episodes (1.4%), and angioedema involving multiple sites was found for 63 episodes (17.2%). Of the episodes involving multiple sites, 21 (33.3%) were types 1 and 2, 21 (33.3%) were types 1 and 3, 9 (14.3%) were types 2 and 3, and 12 (19.0%) were types 1, 2, and 3. Patients were admitted for 213 episodes (58.0%). Admission was required for 52.9% of the type 1 episodes, 47.6% of the type 2 episodes, 40.0% of the type 3 episodes, and 85.7% of the episodes involving multiple sites (66.7% of types 1 and 2, 95.2% of types 1 and 3, 89.9% of types 2 and 3, and 100% of types 1, 2, and 3).

Factors associated with the need for hospital admission are presented in Table 1. Bivariate analysis demonstrated the following to be associated: non-

TABLE 2. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH NEED FOR HOSPITAL ADMISSION

Variable	<i>b</i>	<i>SE</i>	<i>OR</i>	95% <i>CI</i>	Wald χ^2	<i>p</i>
Non-African American	0.98	0.35	2.66	1.35 to 5.24	7.95	0.005*
Allergies	0.83	0.34	2.30	1.19 to 4.47	6.06	0.014*
Alcohol	1.42	0.51	4.12	1.53 to 11.09	7.85	0.005*
ACE or ARB	0.70	0.33	2.01	1.05 to 3.87	4.40	0.036*
Multiple sites	1.93	0.53	6.87	2.44 to 19.34	13.35	<0.001*
Age	0.03	0.01	1.03	1.01 to 1.05	12.09	<0.001*

Multivariate analysis using logistic regression (backward elimination) for 243 episodes with complete data for all potential predictors. Reference category is not requiring admission.

*Statistically significant at $\alpha = 0.05$.

African American race, history of allergies, smoking, alcohol use, use of ACE inhibitors or ARBs, multiple admissions, hoarseness, dysphagia, drooling, multiple affected sites, and age. A logistic regression model was developed evaluating all of the potential predictors suggested by the unadjusted analysis, except for a history of multiple admissions (Table 2). This predictor was not considered because data regarding prior admissions were only available for 158 episodes. The resulting model included non-African American race, allergies, alcohol use, use of ACE inhibitors or ARBs, multiple affected sites, and age as significant predictors of admission. The model accounted for 37% of the variability in the need for admission ($r^2 = 0.37$). An a priori model evaluating non-African American race, history of allergies, use of ACE inhibitors or ARBs, multiple admissions, stridor, dyspnea, drooling, multiple affected sites, age, sex, and history of angioedema as predictors was also evaluated and yielded the identical model except for the inclusion of alcohol use (data not presented).

The mean ($\pm$ SD) length of stay was 2.0 ± 2.4 days, and the range was less than 1 day to 18 days. Eighty-two episodes (22.3%) required admission to the intensive care unit. Three hundred thirty-two episodes (90.5%) were treated with steroids, and 343 (93.5%) were treated with histamine 1 or histamine 2 blockers. Twelve episodes (3.3%) required intubation, and 1 episode (0.3%) required tracheostomy. Four airway interventions were performed immediately, and the rest were performed within 24 hours. All intubations were performed fiberoptically: 11 in the operating room and 1 in the emergency room. Of the 12 episodes that required intubation, isolated type 1 angioedema was found in 2 episodes, isolated type 2 in 1, isolated type 3 in none, and multiple sites in 9 (types 1 and 2 in 1, types 1 and 3 in 3, types 2 and 3 in 3, and types 1, 2, and 3 in 2). The patient who required a tracheostomy had type 1 angioedema involving severe swelling of the oral tongue. The average time to extubation was 1.8 days (range, 1 to 6 days). No patient required reintubation. Bivariate

analysis demonstrated that age, stridor, hoarseness, dyspnea, dysphagia, drooling, and multiple affected sites were associated with airway intervention, but the sample sizes were small (Table 3).

An immunology consultation was obtained for 110 episodes (30.0%), although only 12 had immunologic workups available for review. No diagnoses of hereditary or acquired angioedema or autoimmune disease were made. All patients recovered, except for 1 death not attributed to angioedema.

DISCUSSION

Our review is one of the largest series to date evaluating angioedema, in patients presenting to 3 large, urban tertiary care centers. Our data support prior reports that angioedema occurs more frequent-

TABLE 3. BIVARIATE ANALYSIS PERFORMED WITH CHI-SQUARE OR FISHER'S EXACT TEST FOR CATEGORICAL VARIABLES ASSOCIATED WITH NEED FOR INTUBATION OR TRACHEOSTOMY

Variable	<i>n</i>	<i>OR</i>	95% <i>CI</i>	χ^2	<i>p</i>
Female	367	1.78	0.48 to 6.58	0.76	0.555
Non-African American	332	2.29	0.65 to 8.08	1.74	0.295
Allergies	367	1.19	0.38 to 3.71	0.09	0.772
Smoking	319	0.82	0.17 to 3.86	0.07	1.00
Alcohol	319	0.50	0.06 to 4.02	0.43	1.00
History of angioedema	367	0.71	0.19 to 2.64	0.26	0.763
ACE or ARB	367	2.41	0.73 to 7.96	2.20	0.165
Multiple admissions	158	1.12	0.13 to 9.55	0.01	1.00
Stridor	364	117.0	11.1 to 1236.55	65.23	<0.001*
Hoarseness	337	38.7	4.86 to 307.3	29.89	<0.001*
Dyspnea	359	5.45	1.76 to 16.93	10.56	0.006*
Dysphagia	310	16.34	3.38 to 78.96	20.79	<0.001*
Rash	365	1.03	0.22 to 4.76	0.001	1.00
Drooling	297	22.24	5.17 to 95.6	32.62	<0.001*
Multiple sites	367	12.50	3.72 to 42.04	25.69	<0.001*

For age (continuous variable), *n* was 367, mean difference was 14.93, 95% *CI* was 3.85 to 26.01, *t* (2-tailed) was 2.65, and *p* was 0.008 (statistically significant).

*Statistically significant at $\alpha = 0.05$.

ly in female and African American patients. For almost half of the episodes (47.2%), the patients were on ACE inhibitors at the time of presentation. African Americans were twice as likely to have ACE inhibitor- or ARB-related angioedema as were non-African Americans. Our findings are similar to those of Mahoney and Devaiah,¹¹ who found that African Americans were 3 times as likely to have ACE inhibitor-related angioedema as were other groups. A small number of episodes in our series could be attributed to medications other than ACE inhibitors and ARBs. About 20% of episodes could be attributed to foods, insect bites, fumes, or minor trauma. Multiple causes were found in 7.1%, and 33.5% of the episodes were idiopathic. The causes of angioedema in our series were similar to those in prior reports.

Fifty-eight percent of the episodes required admission — a finding that is also similar to those of prior studies reporting admission rates of 25% to 84%.^{3,9,11-13} On multivariate analysis, age, non-African American race, history of allergies, use of ACE inhibitors or ARBs, alcohol use, and multiple affected sites were associated with the need for admission, whereas symptoms were not. Our model predicted only 37% of the variability in the need for admission, as the clinical course of angioedema is extremely complicated, with multiple potential contributing factors. On multivariate analysis, Banerji et al¹⁷ also found that non-African American race was a significant predictor, but that age was not. Ishoo et al¹³ and Roberts et al¹⁵ found that ACE inhibitor-related angioedema was more severe than angioedema from other causes, as more patients required intensive care unit monitoring.

A high percentage of episodes (75.7%) presented with type 1 (facial or oral cavity) edema. We did not demonstrate a progression of angioedema from superior to inferior sites, as isolated type 2 or 3 angioedema was found in 29.2% of the non-type 1 episodes and angioedema involving noncontiguous sites was found in 33.7% of the non-type 1 episodes. There was little difference in the need for admission and airway intervention for the 3 types of isolated angioedema, but episodes of edema involving multiple sites were more likely to require admission and airway intervention, particularly if laryngeal involvement was present. Chiu et al¹² and Grant et al,⁶ using the initial classification scheme of Chiu et al,¹² found that as angioedema progressed beyond the oral cavity, more patients required admission and airway intervention. Bentsianov et al³ found that patients with laryngeal edema alone and patients with both laryngeal and oropharyngeal edema were more likely to require airway intervention,

whereas Zirkle and Bhattacharyya¹⁴ found that patients with oral cavity or oropharyngeal edema were more likely to require airway intervention. In the present study, the 1 patient who required a tracheostomy had isolated type 1 angioedema. The small number of episodes requiring airway intervention prevented multivariate analysis of potential predictors, but on bivariate analysis, age, symptoms, and multiple affected sites were associated with a need for intervention. A need for vigilance is suggested, as 4 interventions occurred at presentation and 9 occurred within the first 24 hours.

Only a small number of our patients (3.6%) required airway intervention — a finding that differs from previous reports in which between 10% and 34% required intubation or tracheostomy.^{3,6,9,12-14} Given the location of the 3 hospitals and the relatively high percentage of African Americans treated, the emergency rooms at our institution see a very large number of patients presenting with angioedema. Having experienced the unpredictability associated with the clinical course of angioedema, it seems that our emergency room physicians are extremely vigilant with these cases and err on the side of caution with close monitoring and early and aggressive medical treatment. Indeed, the otolaryngology service is frequently involved immediately upon presentation, thus possibly preventing the more serious complications such as airway obstruction. Another possible reason for the lower rates of airway intervention found in our study is that the convenience sample that was used in the chart extraction may have led to selection bias.

The retrospective nature of the study limits the evaluation of treatment options and outcomes. More than 90% of the episodes were treated with intravenous steroids and histamine 1 or histamine 2 blockers. Although these are standard therapies for treatment of angioedema, they are not evidence-based. Current basic science and immunologic evidence suggests that antihistamines and glucocorticoids are relatively ineffective and that patients need to be monitored until the swelling resolves.¹⁸ A prospective, controlled study is required to determine the efficacies of these traditional therapies as opposed to a more observational approach. In addition, new therapies with kallikrein inhibitors and bradykinin type 2 receptor antagonists are currently being evaluated for treatment of hereditary and drug-induced angioedema.¹⁸

As mentioned above, we were unable to extract a consecutive sample of charts at any of the 3 hospitals. The manner in which the medical records were organized and stored made it impossible to obtain

consecutive charts. There is a possibility of some selection bias, as 74% of the episodes occurred in the latter 4 years of the study and the sample drew more heavily from Long Island College Hospital, in which the highest percentage of charts was available for review. However, our sample size is large, the hospitals are located in 1 geographic borough, and many of the clinical services, including the otolaryngology service, cover all 3 hospitals.

CONCLUSIONS

Angioedema involving the upper aerodigestive tract is a potentially life-threatening entity that is

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