Evaluation of the Clinical and Laryngoscopic Findings in Patients with Angio-oedema: An 11-Year Experience at a Single Tertiary Care Centre

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ABSTRACT

Objective: To evaluate the clinical features of angio-oedema (AE) and their correlation with fibre-optic nasolaryngoscopy (FNL) findings.

Methods: The charts of adult AE patients for 225 episodes who were admitted as in-patients from January 2002 through December 2012 were reviewed.

Results: Of the 51 episodes (22.6%) with laryngeal swelling, 16 had exclusively laryngeal swelling; without oropharyngeal swelling. Swelling of the laryngeal structures on FNL was not significantly associated with a suspected aetiology or history of AE or allergies. Dysphagia ($p = 0.033$) and swelling of the posterior pharyngeal wall ($p = 0.011$) were the only clinical features that had a significant positive correlation with laryngeal swelling.

Conclusion: All patients with AE should undergo a FNL examination as part of the initial assessment. Patients with dysphagia and posterior pharyngeal wall swelling on clinical examination has significant positive correlation with laryngeal swelling on scopy examination; hence these patients should be referred to the otolaryngologist and to a facility with intensive care unit care as early as possible for safe management.

Keywords: Angio-oedema, clinical features, fibre-optic nasolaryngoscopy, laryngeal swelling

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INTRODUCTION

Angio-oedema (AE) is an immunologically mediated, anatomically limited, non-pitting oedema. It has a predilection for the mucosal tissue of the upper airway and can therefore lead to life-threatening airway obstruction. Although the exact mechanisms of AE differ depending on the aetiology, the disease is generally caused by increased vascular permeability with extravasation of fluid into the submucosal or subcutaneous tissues as a response to mast-cell-derived vasoactive mediators (1).

The principal cause of morbidity and mortality in patients with AE is airway compromise (1). Previous studies showed that patients with laryngeal and oropharyngeal AE are more likely to be admitted as in-patients and to require airway intervention. In our centre, effective management of AE patients includes, in addition to a routine evaluation, a clinical evaluation with fibre-optic nasolaryngoscopy (FNL). Thus far, few studies have assessed the role of FNL in the management of AE (2) and FNL findings have yet to be correlated with its clinical features. Here we report the results of an 11-year study whose aim was to evaluate the inciting factors, presentation and clinical course of AE and to determine how the FNL findings can contribute to the management of these patients.

MATERIALS AND METHODS

Approval was obtained from the Ethical Committee of the Queen Elizabeth Hospital, Barbados. A retrospective chart review of all patients 18 years of age or older who were seen at the Emergency Department of our hospital between January 2002 and December 2012 was conducted. Angio-oedema patients admitted to the general surgical ward or intensive care unit (ICU) were identified using International Classification of Diseases, ninth version

(ICD-9) code 995.1 (angio-oedema). Patients of African descent who underwent FNL examination and had complete records were included in this study.

The diagnosis of AE was made and confirmed by two specialists, an Accident and Emergency Medicine physician and an otorhinolaryngologist, based on clinical features. All patients in this study were intravenously administered 500 mg of hydrocortisone, 20 mg of famotidine and 50 mg of diphenhydramine as initial treatment.

The patients were assigned to the mild, moderate and severe disease groups according to the severity of their clinical features with respect to AE, the FNL findings and the response to the initial treatment in the emergency department. The decision to admit the patients as in-patients was made by the otorhinolaryngologist based on these categories. Patients with minor symptoms who responded well to initial treatment were considered to have mild disease and were discharged home. Those who did not adequately respond to initial treatment were considered to have moderate disease and were admitted to the hospital's general surgical ward. Patients who had worse clinical symptoms and/or swelling at multiple oropharyngeal sites, significant tongue swelling or any swelling of the laryngeal structures on FNL were judged to have severe disease and were preferentially admitted to ICU.

Oropharyngeal swelling on FNL was defined as swelling at any of the following five sites: the tongue base, uvula, soft palate, vallecula or posterior pharyngeal wall.

Laryngeal swelling was defined as swelling at any of the following ten sites: epiglottis, arytenoids, aryepiglottic folds, post-arytenoid, Supraglottic region, post-cricoid, Supraglottic fold, true cords, false cords or pyriform fossa. Fibre-optic nasolaryngoscopy was repeated by the otorhinolaryngologist at six and 24 hours after the initial examination. In patients with severe clinical features and significant findings on the initial examination, FNL was repeated more frequently to evaluate progression and response to management.

(All FNL examinations were performed by the otorhinolaryngologist, who had more than three years of experience).

The data retrieved from the charts included demographic variables (age, gender and race), clinical variables (symptoms, anatomical distribution of the AE), details of the FNL findings at the initial examination, pertinent medical, surgical and family history (such as allergies and AE), and any pre-hospital treatment received, treatment provided in-hospital, airway interventions, results of any allergen tests, length of ICU stay, total length of hospital stay and the outcome of the admission.

Statistical analysis was performed using SPSS Statistics version 18. Demographic data and correlations were analysed using descriptive statistics. An association between categorical variables was assessed using Pearson's $\chi 2$ test or Fisher's exact test. A two-tailed *t*-test was used to analyse continuous variables. Factors that were significant on univariate analyses were entered into a multivariate logistic regression model to identify the clinical features that predict laryngeal swelling. A p-value ≤ 0.05 was considered to indicate statistical significance.

RESULTS AND ANALYSIS

Over the 11-year period, 442 episodes of AE presented to the Accident and Emergency Department. Of these, 299 (67.6%) had moderate or severe disease and were admitted as in-patients for further management. Two episodes were excluded from the study so that the study population would consist only of patients of African descent; a further 19 episodes were excluded because of incomplete records. Of the remaining 278 episodes, complete FNL exams were available for 225. These 225 charts were analysed and formed the basis of this study. Demographic and aetiological variables are shown in Table 1.

Table 1: Demographic profile, aetiological factors and comorbid conditions for angio-oedema (n = 225)

Variable	**n (%)**
Age ≥ 65 years	106 (47.1%)
Sex	
Male	70 (31.1%)
Female	155 (68.8%)
Suspected aetiology	
Food	16 (07.1%)
ACEi	111(49.3%)
ARB	18 (08.0%)
NSAID	12 (05.3%)
Aspirin	39 (17.3%)
Beta blockers	53 (23.5%)
Diuretics	97 (43.1%)
Co-morbid conditions	
HTN	180 (80.0%)
Diabetes	74 (32.8%)
CAD	35 (14.2%)
Asthma	15 (06.6%)
History of previous angio-oedema	66 (29.3%)
History of allergies	66 (29.3%)
Multiple admissions	22 (09.7%)

All 225 episodes were for patients of African descent (Afro-Caribbean)
ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CAD = coronary artery disease; HTN = hypertension; NSAID = nonsteroidal anti-inflammatory drugs

In this review, 68.8% (n =155) of the episodes occurred in female patients. The mean age of the 155 episodes for female and 70 episodes for male patients was 61.94 years (SD ± 19.03) and 54.47 years (SD ± 17.99), respectively. The difference in the mean ages of the female and male patients was significant (*t*-test $p = 0.006$). Patients 65 years and older accounted for 47.11% (n = 106) of the cases. Presentation to the Emergency Department

within < 6 hours from the onset of symptoms was documented in 40.4 % (n = 91) of the episodes; in 48.5 % (n = 109), presentation was between six and 24 hours; and in the remaining 11.1% (n = 25) after 24 hours. Admission to the ICU was required for 93 (41.33%) episodes; in the remaining 132 (58.66%) episodes patients were admitted to the general surgical ward. In 22 episodes, the AE was a recurrence (≥ 2 episodes); in the remaining 203 episodes, hospital admission was for a first episode of AE.

The frequencies of the clinical features are shown in Table 2.

Table 2: Angio-oedema and the frequency of clinical features (n = 225)

Clinical feature	**n (%)**
Lip swelling	88 (39.1%)
Face swelling	58 (25.7%)
Floor of mouth swelling	104 (46.2%)
Tongue swelling	153 (68.0%)
Palate swelling	31 (13.7%)
Uvula swelling	53 (23.5%)
Dyspnoea	37 (16.4%)
Dysphagia	80 (35.5%)
Voice change	55 (24.4%)
Stridor	01 (0.4%)

Only 5 (2.22%) episodes of the 225 episodes required airway instrumentation, all in the form of a tracheotomy. Details of the FNL findings are provided in Table 3.

Table 3: Fibre-optic nasolaryngoscopy (FNL) findings (n = 225)

Site of swelling on FNL	**n (%)**
Oropharyngeal sites	
Tongue base	73 (32.4%)
Uvula	41 (18.2%)
Posterior pharyngeal wall	36 (16.0%)
Soft palate	25 (11.1%)
Vallecula	28 (12.4%)
Site of laryngeal swelling	
Epiglottis	24 (10.6%)
Arytenoids	24 (10.6%)
Aryepiglottic fold	15 (06.6%)
False cords	14 (06.2%)
Supraglottic region	07 (03.1%)
Post-arytenoid	05 (02.2%)
Supraglottic fold	03 (01.3%)
True cords	03 (01.3%)
Post-cricoids	03 (01.3%)
Pyriform fossa	01 (00.4%)
Number of laryngeal sites swollen	
Swelling at one laryngeal site	25 (11.1%)
Swelling at ≥ two laryngeal sites	26 (11.5%)

The FNL examination identified laryngeal and/or oropharyngeal swelling in 50.2% (n = 113) of episodes. Swelling was confined to the oropharyngeal area in 62 (27.5%) and to the laryngeal structures in 16 (7.1%) episodes. The remaining 35 (15.5 %) episodes patients

had swelling of both the laryngeal and the oropharyngeal areas. On FNL, the most common site of oropharyngeal swelling was the base of the tongue (n = 73, 32.4%).

The most common sites of laryngeal swelling were the arytenoids, epiglottis, false cords and aryepiglottic folds. Laryngeal swelling, either alone or together with oropharyngeal swelling, occurred in 51 (22.6%) episodes. Laryngeal swelling as seen on FNL was not significantly associated with patient age, use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), chronic illnesses (hypertension, diabetes) or a history of AE or allergies. The relationship between clinical features and laryngeal swelling is shown in Table 4.

Table 4: Logistic regression analysis of the relationship between the clinical features of angio-oedema and laryngeal swelling as seen on fibre-optic nasolaryngoscopy

			95% confidence level for Exp (B)	
Variable	**Significance**	**Hazard ratio**	**Lower limit**	**Upper limit**
Lip swelling	0.020	0.416	0.199	0.869
Uvula swelling	0.160	1.728	0.806	3.705
Posterior pharyngeal wall swelling	0.011	3.605	1.343	9.678
Dysphagia	0.033	2.077	1.059	4.072
Constant	0.000	0.213		

There was no significant positive correlation between any of the clinical features and laryngeal swelling, except for dysphagia (p = 0.033) and swelling of the posterior pharyngeal wall (p = 0.011). Swelling of the lips correlated negatively with laryngeal swelling (p = 0.020). The mean length of hospital stay for the 225 episodes was 2.63 ± 1.11 days

(median = 2.00 days). The mean length of stay in the ICU for the 93 episodes was 1.15 ± 0.50 days.

DISCUSSION

This review was based on the largest series to date of patients of African descent who presented to a single centre with AE, which was evaluated by a routine examination and a FNL examination to assess oropharyngeal and laryngeal swelling. Additionally, this was the largest study to evaluate the clinical and laryngoscopic findings of patients with AE.

Many of our findings are in line with those published in the literature, including the predominance of female patients [66.6%] (3, 4). More than half (57.3%) of the overall admissions and over two-thirds (68.4%) of the ICU admissions involved patients using ACEi or ARB. Worldwide, ACEi were shown to be a major aetiological factor for AE (5) and the incidence of AE development in patients on ACEi is estimated to be 0.1–0.7% (6–10). While this is a significant number of cases, the incidence is still considered to be very low and the multiple benefits of these drugs significantly outweigh the risk of developing AE. However, these drugs should be withheld, whenever possible, in patients who develop AE.

Among the common presenting features of AE are swelling of the facial and/or pharyngeal structures. Facial swelling is not life-threatening but in one series swelling of the larynx and upper airway was life threatening in up to 20% of the cases (6). Early signs of laryngeal oedema may include hoarseness and inspiratory stridor, which may progress to airway obstruction in up to 10% of the cases (3, 11). Clinical signs clearly associated with laryngeal swelling include voice change, dysphonia, hoarseness and strider (12, 13).

The incidence of laryngeal swelling in our study was similar to that reported in the literature. In a review of 133 cases of AE by McCormick *et al*, laryngeal swelling was found

in 22% (1). Ishoo *et al*, reported laryngeal swelling in 33% of the 93 reviewed cases of AE (12). In our series, laryngeal swelling was diagnosed in 51 (22.6%) of the 225 episodes who underwent FNL.

Fibre-optic nasolaryngoscopy has become an increasingly important part of the management of AE. To our knowledge, the only study to report the details of laryngeal swellings was that of Al-khudaria *et al* (13). In their 40 patients with AE, swelling at the aryepiglottic folds, lingual epiglottis and laryngeal epiglottis was detected in 50%, 22.5% and 12.5%, respectively, of the patients (13). In our study, the most common locations of laryngeal swelling were the epiglottis and arytenoids (n = 24, 10.6% for each site) followed by the aryepiglottic fold (n = 15, 6.6%).

One of the benefits of analysing laryngoscopy data is the opportunity to investigate the relationship between the clinical findings on the initial physical examination and the presence of laryngeal swelling on laryngoscopy. The logistic regression analysis with backward elimination model used in this study identified two clinical features that independently predicted laryngeal swelling: posterior pharyngeal wall swelling (p = 0.011) and dysphagia (p = 0.033). Conversely, there was a negative correlation between swelling of the lips and laryngeal swelling (p = 0.020).

On clinical examination, posterior pharyngeal wall swelling was observed in 25 episodes, which suggests that this is an important clinical feature that should be carefully evaluated. Not only did it predict laryngeal swelling but it was also associated with a higher likelihood of ICU admission (18 out of the 25 episodes). A similar association between posterior pharyngeal and uvular swelling and laryngeal swelling was reported by Al-Khudari *et al* (13) and Ishoo *et al* (12).

Dysphagia was the other clinical feature that correlated with laryngeal swelling in our study. Swallowing is a complex function that involves the coordination of oropharyngeal

structures, the larynx and the oesophagus and requires open passageways. Dysphagia and drooling of saliva can be signs of swelling of the tongue base or of other oropharyngeal structures, but according to our results they also indicate laryngeal swelling. This may explain why patients presenting with tongue swelling and an inability to manage their oral secretions have a significantly higher rate of hospital admission and airway intervention (14) Therefore, these patients should be carefully observed and a low threshold for endotracheal intubation established (11).

A negative correlation between lip swelling and laryngeal swelling (p = 0.020) was also reported by Al Khudari *et al* (13) and McCormick *et al* (1). The pathophysiology underlying this finding is not well understood. However, this correlation should be interpreted carefully, as patients with lip swelling may still have laryngeal swelling on presentation. In these cases, laryngoscopy is still recommended for the safe management of patients with AE (1).

The airway intervention rates in several other studies ranged from 3.6% to 29 % (1, 3, 11, 13, 15). Laryngeal involvement is generally considered to be a predictor for the early implementation of airway control, although the exact laryngoscopy findings that indicate the need for airway intervention are unknown. Moreover, a significant number of airway interventions are done on clinical grounds, even before either a complete evaluation of the airway or even FNL.

In the management of AE of the head and neck, among the options for securing the airway in the spontaneously breathing patient, fibre-optic bronchoscope (FOB) intubation is the method preferred by most clinicians and considered as gold standard. Other possibilities are intubation by performing direct laryngoscopy and a surgical airway. The choice depends on the specifics of the case but the chosen method of airway management should be the one that is safest and can be performed with available resources and in accordance with the

expertise of the team on duty. In our study, five episodes (2.22%) needed airway intervention, which in all cases consisted of tracheotomy. These five episodes patients had AE involvement at multiple sites, including significant swelling of the tongue and glottis involvement. In our opinion, one of the main reasons for the low incidence of airway interventions in this study was the routine inclusion of a FNL examination as a part of the initial evaluation to stratify management. The use of FNL in the initial evaluation of AE allows an objective assessment of the airway and thus may reduce the number of airway interventions and their associated complications. Therefore, an early FNL examination can contribute significantly to the safety and successful recovery of the patient.

The limitations of this study include its retrospective nature. Also, we were unable to obtain the details of FNL data for 53 episodes, as FNL records incomplete. These patients were excluded from the study.

CONCLUSIONS

In patients with AE, the presence of dysphagia and posterior pharyngeal wall swelling on clinical examination correlate significantly with laryngeal swelling on FNL examination. We therefore recommend that, for the safe management of AE patients, all those with dysphagia or posterior pharyngeal wall swelling on clinical examination be referred to an otolaryngologist and to a facility with intensive care unit care as early as possible for FNL evaluation of the airway.

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AUTHORS' NOTE

The English in this document has been checked by at least two professional editors, both native speakers of English.

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