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Angioedema: 6 years experience with fourteen cases

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Abstract

Objective: To study the difference in the findings between the causes of angioedema and the characteristics of angioedema induced by angiotensin receptor II blockers (ARBs), and to investigate whether laboratory examinations for acute phase inflammatory markers can aid in diagnosis and predict airway risk.

Methods: We retrospectively reviewed fourteen cases of patients with angioedema that were treated from 2000 to 2006. Data were collected regarding age, sex, location of the edema, cause, time course of resolution and laboratory examinations (leukocyte counts, serum C-reactive protein (CRP) level, complement function and the activity of C1 esterase inhibitor).

Results: The causes of angioedema were ACEIs in six patients (42.9%), candesartan (ARB) in three (21.4%), HAE (types 1 and 2) in two, and unknown in three. Of these patients, 71.4% exhibited edema in the floor of the mouth, irrespective of the cause. Two patients with edema induced by candesartan exhibited both lingual and laryngeal edemas. The remaining one with candesartan-induced edema exhibited edema in the neck and mediastinum and pleural effusion.

The average time to resolution was 4.1 days, ranging from one to twelve days. The edema in eleven patients resolved with conservative therapy, while three patients underwent tracheotomy. In two patients with candesartan-induced edema, although the edemas resolved completely after cessation of candesartan administration, the edemas reappeared in the same locations, two and thirty days after the cessation of candesartan for each patient.

None of the patients with angioedema induced by ACEIs exhibited elevation of serum CRP levels. No significant differences were found for leukocyte counts and serum CRP levels between patients with angioedemas induced by ACEIs, ARB and those of unknown cause. No significant differences were observed in the above findings between the patients who underwent tracheotomy and those who did not. Two patients exhibited low C4 levels, and one of the two exhibited no activity of C1 esterase inhibitor.

Conclusion: Consistent with previous reports, angioedema in the floor of the mouth extending to the tongue should be considered as a possible risk factor for airway compromise. Laboratory examinations for acute phase inflammatory markers are not useful for diagnosis and are not predictive for airway intubation and tracheotomy. Angioedema induced by candesartan can present in anomalous sites and reappear following drug cessation even if the edema has resolved completely.

Keywords: Angioedema; Angiotensin converting enzyme inhibitor (ACEI); Angiotensin II receptor blocker (ARB); Tracheotomy

1. Introduction

Angioedema is a non-pitting edema that occurs in the skin and mucous membranes. It is characterized as a disorder with an anatomically limited acute onset, which may potentially affect any part of the body but is usually confined to the head and neck. Because of the rapid and potentially devastating clinical course, angioedema of the pharynx and larynx may lead to life-threatening situations and often require emergency treatment. Therefore, it is important to determine the criteria that will allow the identification of patients at risk of progressive airway compromise. Some researchers have shown that airway risk

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in angioedema could be predicted by the anatomic site of presentation [1–3]. There are a multitude of precipitating factors, such as hereditary deficiency of C1 esterase inhibitors (hereditary angioedema: HAE), temperature extremes, trauma, food sensitivity, and medications, such as penicillin and aspirin [4]. In recent years, the use of angiotensin converting enzyme (ACE) inhibitors (ACEIs) has become the leading cause of angioedema. The incidence of ACEI-related angioedema has increased from 0.1–0.2% to 1% over the last decade [4–7]. ACE is the enzyme that converts both angiotensin I to angiotensin II, the most potent vasoconstrictor agent, and metabolizes bradykinin, a vasodilating agent. Thus, ACEIs block the production of angiotensin II, resulting in a net vasodilatation, which causes an antihypertensive effect, and blocks the degradation of bradykinin, resulting in elevated bradykinin levels and increased capillary permeability that produces angioedema [8]. Angiotensin receptor II blockers (ARBs) are a new class of effective antihypertensive drugs. ARBs act at the receptor site and do not affect ACE; hence, bradykinin levels should theoretically remain unaffected. However, sporadic case reports have described angioedema related to ARBs [9–13]. Losartan, an ARB, has recently been shown to increase serum bradykinin levels [14]. Thus, bradykinin is known to play a major role in the pathophysiology of ACEI-induced, and likely also in ARB-induced angioedemas, similar to that of angioedema caused by C1 esterase inhibitor deficiency [15–17]. Complement component analysis is valuable for differentiating the various types of angioedema, such as HAE, and the acquired type of C1 esterase inhibitor deficiency [18]. Recently Bas et al. reported that patients treated with ACEI exhibited increased plasma levels of C-reactive protein (CRP) and fibrinogen [19]. However, no reports have described the differences in the characteristics of angioedema depending on inciting causes, except for these two reports.

In this paper, we reviewed fourteen patients with angioedema that we diagnosed and treated during a 6-year interval. Eleven patients resolved with conservative treatment, while three patients underwent tracheotomy despite the administration of steroids. The most frequent site of presentation was floor of the mouth, regardless of the inciting cause. The patients with edema induced by candesartan (ARB) exhibited an anomalous clinical course. We assessed the differences in the findings depending on the causes of angioedema. Furthermore, we also report the characteristics of angioedema induced by ARBs, compared with the findings of angioedemas induced by ACEIs.

2. Methods

The records of the patients who were admitted to the Department of Otolaryngology-Head and Neck Surgery, Kyoto Prefectural University of Medicine, Department of Otolaryngology, Omihachiman Municipal Hospital and Department of Otolaryngology, Rokujizo General Hospital between June 2000 and September 2006 were reviewed. The patients' records were reviewed for age, sex, location of the edema, cause, and time course of resolution. We also reviewed laboratory examinations (leukocyte counts, serum CRP level, complement function and the activity of C1 esterase inhibitor) as in the reports of Brasher et al. [18] and Bas et al. [19].

3. Results

The fourteen Japanese patients included seven females and seven males, with a median age of 64.9 years, ranging from 48 to 79 years. Table 1 shows a summary of the patients' characteristics.

4. Causes

ACEIs were the cause of angioedema in six patients (42.9%). Candesartan (ARB) was the cause in three patients (21.4%). Two patients suffered from HAE (patient 10, type 1; patient 13, type 2). The other causes of angioedema in the remaining three patients were unknown.

5. Locations of the edema

The majority of patients (71.4%) exhibited edema in the mouth, particularly the floor of the mouth, irrespective of the cause. All of the patients with angioedema induced by ACEIs exhibited edema in the floor of the mouth (Fig. 1). Three patients (1–3) who underwent tracheotomy exhibited edemas that extended from the floor of the mouth to the tongue. Candesartan-induced angioedemas were observed in various regions. Patients 11 and 12 exhibited laryngeal and lingual edemas, respectively. Patient 4 exhibited edema in the neck and mediastinum, and pleural effusion (Fig. 2a and b). Table 1 also shows the locations of the edema in the other patients.

6. Time course of resolution

Steroid (methyl-predonisolone or hydrocortisone) was administered to all of the patients, except for patient 4. Antihistamines were also administered to all of the patients. The edema in eleven of the patients resolved with conservative therapy, while three patients underwent tracheotomy although steroids were administered rapidly. The edema in the floor of the mouth resolved immediately after the steroid administration among patients 6–9, 13 and 14. The edema in floor of the mouth resolved for one day in patients 8 and 9, while it took longer to resolve in the neck, penis and basal tongue. The average number of days to resolution was 4.1 days, ranging from one to twelve days.