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Antihypertensive drug-induced angioedema causing upper airway obstruction in children

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ABSTRACT

Objective: Angioedema is a well-described complication arising from the use of antihypertensive agents in the adult population. However, its occurrence and potential for upper airway compromise in pediatrics has only been sporadically reported in the literature. Our objective is to report and review the occurrence of antihypertensive-induced angioedema in the pediatric population and the potential for airway compromise.

Methods: Charts of 42 patients admitted to Cincinnati Children's Hospital Medical Center with the discharge diagnosis of angioedema (ICD-9 code 995.1) from January 2000 to January 2010 were reviewed. Of the 42 charts, 3 cases had angioedema induced by antihypertensive drugs and all 3 resulted in upper airway obstruction. Summary and findings of the data collected from the medical chart review included demographics, chief complaint(s), past medical history, hospital course, antihypertensive drugs used, diagnostic test(s), medical treatment, and time from onset of symptoms to resolution. In addition, a PubMed literature search using the terms angioedema and antihypertensive drugs was performed to review its occurrence in pediatrics. The previous literature case reports were compared to our cases to further characterize and emphasize the clinical features of this occurrence in children and adolescents.

Results: Despite the well-known occurrence of antihypertensive drug-induced angioedema causing airway obstruction in adults, only 4 case reports have been previously published in children. At our institution, we describe 3 children who developed acute angioedema with upper airway obstruction after the chronic use of antihypertensive medications [2 drugs in the ACE inhibitor class (enalapril and lisinopril), and 1 drug in the calcium channel blocker class (CCB; amlodipine)]. In all 3 cases, the symptoms resolved within 1 week after the antihypertensive agent was discontinued.

Conclusion: Upper airway obstruction can occur at any age when taking antihypertensive drugs. Particular caution should be applied to ACE inhibitors and CCBs in this regard. With the increasing use of antihypertensive agents in the pediatric population, clinicians should be alert to the possibility of angioedema with upper airway obstruction as a potential lethal adverse effect.

1. Introduction

The occurrence of obesity in children and adolescents in the United States has more than tripled over the last 30 years [1]. In parallel with increases in body mass index in childhood, the prevalence of hypertension in children and adolescents has also risen over the past decade, with the current incidence between 2% and 5%[2–4]. As a result, the use of antihypertensive medications in this young population has become widespread and will most likely continue to increase [5].

Antihypertensive medications, most notably angiotensin-converting enzyme (ACE) inhibitors, have been widely described in the adult population as potential inducers of angioedema. In adults, they are the most common drug class precipitating angioedema, with an overall occurrence of 0.1–2.2%, followed by angiotensin receptor blockers (ARBs), with an incidence of less than 0.1% [6]. Angioedema is characterized as an acute onset of asymmetrical, self-limited non-pitting swelling in the subcutaneous, cutaneous and mucosal tissues [7,8]. This uncommon, but potentially fatal side effect is anatomically limited, manifesting mostly in the head and neck region and usually involves the face, lips, tongue, and larynx. In rare cases, it can lead to life threatening upper airway obstruction if untreated [8,9,10]. The tissue swelling is believed to

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result from the leakage of fluid into the interstitial space due to mast cell-derived vasoactive mediators, histamine and proteases, with bradykinin playing a major role [8]. As the course of angioedema can be unpredictable and may progress rapidly, it is essential for clinicians to promptly recognize is symptoms and institute treatment to avoid potential life-threatening upper airway obstruction.

Although angioedema is a well-described complication of antihypertensive agents in the adult population, its occurrence and potential for upper airway compromise has only been sporadically reported in the pediatric population. Most cases of angioedema from antihypertensive agents are mild and are treated by discontinuing the offending drug [7,11]. In this study, we report on a single institution experience of antihypertensive-induced angioedema causing upper airway obstruction in children and adolescents and review the literature on this topic.

2. Methods

A retrospective chart review was conducted on all patients admitted to Cincinnati Children's Hospital Medical Center (CCHMC) with the discharge diagnosis of angioedema (ICD-9 code 995.1) between January 2000 and January 2010. Approval for this study was granted by the CCHMC Institutional Review Board. All of the charts were reviewed for documentation of chief complaint(s), past medical history, hospital course, diagnostic test(s), and medical treatment. Age, gender, ethnicity, prior history of angioedema, nature of the presumed inducing agent, and duration of symptoms from onset to resolution were also obtained from the charts.

In identified cases of antihypertensive induced angioedema, the type of antihypertensive drug and duration of therapy were recorded. Emphasis was placed on patients' initial presentation and symptoms, as well as the site of the edema in the upper airway.

In addition, a literature search in PubMed was performed on the terms angioedema and antihypertensive drugs to review its occurrence. The previous literature case reports were compared to our cases to further characterize and emphasize the clinical features of this occurrence in children and adolescents.

3. Results

A total of 42 patients had the discharge diagnosis of angioedema (ICD-9 code 995.1) during the 10-year period. Of those, 3 cases developed acute angioedema resulting in upper airway obstruction after chronic use of the antihypertensive medications, enalapril (ACE inhibitor), amlodipine (calcium channel blockers, CCBs), and lisinopril (ACE inhibitor). Other likely triggers of angioedema, i.e., trauma, food allergies, and other medications were eliminated as potential causes. In all 3 cases, the symptoms resolved within several days after the antihypertensive agent was discontinued. Prompt diagnosis and treatment of antihypertensive-induced angioedema prevented further upper airway compromise in each of these cases. All 3 cases had been taking their antihypertensive medication for over a year without any prior episodes of angioedema. These cases are summarized in Table 1.

4. Case reports

4.1. Case 1

A one-year, 11-month-old African American male with trisomy 21 had a 3-day history of facial swelling and a 1-day history of increasing difficulty breathing. He had no fever, sweats, or recent oral procedures. He had no known drug or food allergies. His family history was not significant. His past medical history was significant for an atrio-ventricular septal defect repair at 6-months of age, with residual mitral valve insufficiency and hypertension. His admission medications were enalapril, flovent and zantac.

On presentation to the emergency room he was stridorous with no wheezing in moderate respiratory distress with subcostal chest retractions. He had low blood pressure and his oxygen saturation was 70%. He had significant oropharyngeal facial and neck edema. The lung exam revealed clear breath sounds bilaterally. With a presumed diagnosis of acute anaphylaxis of unknown cause, he was treated immediately with supplemental oxygen, a normal saline bolus, subcutaneous epinephrine, steroids, and IV diphenhydramine. His chest X-ray showed no acute changes. After he was stabilized, he was admitted for further observation, however his oral and facial swelling persisted. His full immune work-up (including immune-globulins and RAST testing for peanuts, soy, wheat, egg yolk, egg white, and celery) was negative except for an elevated IgA level, consistent with a concomitant viral syndrome.

On hospital day 2, after consultation with the Allergy and Cardiology services, enalapril was discontinued with immediate improvement in his facial swelling. On hospital day 6, the patient was discharged with complete resolution of all symptoms.

4.2. Case 2

A 2-year, 6-month-old Hispanic male had a history of recurrent intermittent stridor over 3 months prior to admission. He had no history of fever, sweats, or recent oral procedures. His past medical history was significant for stage 4 hepatoblastoma, and he was 13 months post liver transplant. He did have hypertension secondary to his immunosuppressive medication and was being treated with amlodipine. He had no known drug allergies and his immunization status was up to date.

After undergoing a chest CT scan under general anesthesia for a previous lung nodule, he developed upper airway swelling and stridor. The otolaryngology service was urgently consulted to evaluate his upper airway obstruction. Flexible fiberoptic nasopharyngeal laryngoscopy exam showed "watery edema" of his arytenoids and epiglottis, consistent with angioedema. The angioedema was believed to be secondary to amlodipine and the drug was discontinued.

He was treated with IV dexamethasone, epinephrine, and supplemental oxygen. After discontinuing amlodipine, he had complete resolution of his respiratory distress and was discharged on hospital day 3.

4.3. Case 3

An 18-year-old Caucasian male presented with a sensation of "feeling something in his throat" with lip, eye, and left face swelling. Five days prior to presentation, he had developed hives on his buttocks and lower legs, and left periorbital swelling, for which he had been prescribed oral prednisone. He had a 6-year history of hypertension treated with lisinopril.

In the emergency room, he had no respiratory distress with vital signs normal. His exam showed lip, eye, and left oropharyngeal swelling and diffuse neck swelling. An urticarial rash was also noted on his left lower leg. He was treated with epinephrine, methylprednisolone, and IV diphenhydramine. Soft tissue neck films demonstrated nonspecific right neck soft tissue swelling.

He was admitted with a working diagnosis of drug-induced angioedema, and lisinopril was discontinued. Over 24 h, his symptoms and clinical signs resolved. After consultation with the Allergy and Cardiology services, amlodipine was commenced for blood pressure control. He was discharged on hospital day 2 on amlodipine, prednisone, and claritin.