

Vespa venom allergy, venom immunotherapy was recommended, and our patient was instructed to carry an emergency kit for self-administration.

How can a mucosal sting pass unnoticed by a healthy 27-year-old? Whereas the oral cavity and upper esophagus possess somatic mucosal innervation, visceral afferent activity from the distal esophagus and stomach does not reach higher brain centers and may not be consciously perceived.³ After its ingestion within a bolus of liquid, the insect was presumably flushed down at least to the midesophagus before getting a chance to sting. As a result, systemic anaphylaxis developed without any perception of being stung. Proximal esophageal Hymenoptera stings have occasionally been reported as a cause of local pain and swelling.^{4,5} There are currently no reports of painless deep esophageal or gastric Hymenoptera stings, which are likely to pass unnoticed if not in the context of a systemic anaphylactic reaction and may easily be ignored even if anaphylaxis occurs. Without discovery of a vomited yellowjacket, the cause of anaphylaxis would have remained obscure in this patient, and a misdiagnosis of idiopathic anaphylaxis

might have been made. After exclusion of food allergy, esophageal insect stings should be considered when an unexplained anaphylactic episode occurs after open-air consumption of food or drinks during insect season.

Johanna Stoevesandt, MD

Natalie Grundmeier, MD

Axel Trautmann, MD

Department of Dermatology, Venereology, and Allergology

University of Würzburg

Würzburg, Germany

Stoevesandt_J@klinik.uni-wuerzburg.de

References

- [1] Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S161–S181.
- [2] Golden DB, Moffitt J, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol*. 2011;127:852–854, e1–e23.
- [3] Brock C, Arendt-Nielsen L, Wilder-Smith O, Drewes AM. Sensory testing of the human gastrointestinal tract. *World J Gastroenterol*. 2009;15:151–159.
- [4] Farivar M. Bee sting of the esophagus. *N Engl J Med*. 1981;305:1020.
- [5] Kessler P, Schoenemann J. Unusual summertime foreign body in the esophagus. *Endoscopy*. 1999;31:S24.

Successful C1 inhibitor prophylaxis during zenker diverticulum repair in a patient with hereditary angioedema

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by C1 inhibitor protein deficiency characterized by recurrent episodes of angioedema of the skin, laryngeal edema, or abdominal pain due to gastrointestinal mucosal swelling.^{1,2} Usually self-limiting, it can become life-threatening with airway involvement; up to 25% to 40% of untreated patients with laryngeal edema experience asphyxiation and death.^{1,3} Trauma, including surgically induced trauma, especially involving endotracheal intubation or manipulation, may trigger life-threatening laryngeal edema.⁴ Therefore, appropriate short-term prophylactic therapy should be administered to avoid complications.

Short-term prophylaxis has traditionally involved administration of fresh frozen plasma (FFP), attenuated androgens, and antifibrinolytic agents; however, their side effect profile limits their use.^{5,6} C1 inhibitor (C1-INH) has approval from the Food and Drug Administration for short-term treatment of angioedema attacks and long-term prophylactic therapy but not for short-term prophylaxis.⁷ We describe a case of successful perioperative treatment of a patient with HAE using C1-INH as short-term prophylactic therapy before Zenker diverticulum repair.

A 74-year-old woman with type 1 HAE and Zenker diverticulum was scheduled for an upcoming surgical diverticulectomy. The patient reported onset of angioedema at the age of 8 years. Previous attacks consisted of abdominal pain and facial, throat, hand, and feet angioedema. Exacerbation of symptoms occurred after dental extractions. At the age of 55 years, she was diagnosed as having HAE type 1 and was given danazol for long-term prophylaxis. Her symptoms improved with the medication; however, she continued to experience occasional breakthrough angioedema and abdominal pain. Her most recent attack consisted of neck and laryngeal swelling 6 months before presentation. She had a history of receiving FFP for short-term prophylaxis before cholecystectomy. At that time, she developed a generalized rash after receiving FFP, and cholecystectomy was deferred.

Because of worsening symptoms of food sticking in her throat and inability to swallow hard foods, she was scheduled to undergo surgical

repair of the Zenker diverticulum. She was referred to our allergy clinic for preoperative HAE optimization. One month before surgery, danazol was increased from 200 mg daily to 200 mg twice daily. Subsequently, her C1-INH titers increased from 1:2 to 1:8 (reference range, 1:4–1:16), and her C4 levels increased from 15 mg/dL to 17 mg/dL (reference range, 16–56 mg/dL). Although C1-INH levels normalized before surgery, she was still at risk of an HAE attack, especially because of her upcoming surgery, a known trigger of HAE, given her history of breakthrough angioedema while taking danazol. Thus, she was premedicated with prednisone and diphenhydramine, and she received 1,000 U of C1-INH for short-term prophylaxis on the morning before surgery. The surgery was uncomplicated, and the patient tolerated the procedure well. She did not develop symptoms of angioedema during or after the surgery. Danazol for long-term prophylaxis was continued at 200 mg twice daily. One month after Zenker diverticulectomy, she reported improved swallowing and resolution of throat discomfort and no episodes of angioedema.

Angioedema in HAE is mediated by overproduction of bradykinin that occurs due to nonfunctional or insufficient C1-INH protein, resulting in ineffective modulation of the kallikrein cascade.⁷ It is characterized by recurrent episodes of nonpitting, nonpruritic edema of the extremity, face, trunk, or genitalia, laryngeal edema, or abdominal pain due to gastrointestinal mucosal swelling.^{1,2} Symptoms occur at variable frequency and usually start at an early age. Surgery is an exogenous trigger known to exacerbate HAE, resulting in patient avoidance of procedures. Effective short-term perioperative prophylaxis allows patients to safely undergo interventions.

C1-INH replacement therapy has been effective in mitigating acute attacks and decreasing frequency of attacks as long-term prophylaxis, although procedure-specific short-term prophylaxis has not been evaluated.⁸ Several cases reported in the literature demonstrate the effectiveness and safety of short-term preoperative prophylaxis using C1-INH (Table 1). To date, no reports in the medical literature discuss the use of C1-INH as perioperative management in the setting of major surgery involving the distal pharynx and esophagus. To our knowledge, this case represents the first successful case of short-term C1-INH prophylaxis in the setting of Zenker diverticulum repair.

Table 1
Review of cases in medical literature using C1-INH for short-term perioperative prophylaxis. Seventeen relevant articles were found consisting of case reports or case series. Twelve of seventeen articles demonstrate successful use of C1-INH for short-term perioperative prophylaxis

Case report	Surgical procedure	C1 INH dosing	Post-op complications/Comments
Burke, S. et al. 2011 ⁹	Tracheal dilation	1000 units preprocedural	Bilateral submandibular swelling occurred 1.5 hours after procedure resolved with ecallantide.
Bernstein, Coleman et al. 2010 ¹⁰	1) Pericardiocentesis 2) Cardiac cath	1000 units preprocedural 1000 units 6 hours preprocedural	
Czaller, Visy et al. 2010 ¹¹	3) Mitral valve reconstruction 1) 9 cases of Caesarean or Vaginal Delivery 2) 6 cases of Artificial abortion	1000 units 12 hours preoperatively 500 units preprocedural 500 units preoperatively	
Saito, Namura et al. 2010 ¹²	Mitral valvuloplasty, tricuspid annuloplasty, maze operation and cardiopulmonary bypass	1000 units administered the evening before and immediately preoperatively	
Libert, Scherier et al. 2009 ¹³	Vaginal delivery	500 units preprocedural	
Codispote, Rezvani et al. 2008 ¹⁴	Mitral valve reconstruction with annuloplasty and cardiopulmonary bypass	1000 units 1 hour preoperatively	Postop day 2: lower back and lip swelling treated with 1000 units C1-INH. Symptoms resolved within 2 hours.
Nathani, Sullivan et al. 2006 ¹⁵	Vaginal delivery	1000 units during active phase of labor and artificial rupture of membranes; 1 dose during time of delivery	Postnatal course: leg swelling treated with 500 units C1-INH.
Cace, Brusich et al. 2005 ¹⁶	Ventricular septal defect repair with cardiopulmonary bypass	500 units 2 hours preoperatively	Postop day 2: urethral submucosal edema treated with 500 units C1-INH.
Maeda, Miyawaki et al. 2003 ¹⁷	Extraction of left lower 3 rd molar	500 units postoperatively	
Alonso and Fas 2002 ¹⁸	Cystoscopy and transurethral resection of malignant bladder tumor	500 units 1 hour preoperatively	
Jabbour-Khoury, Khoury et al. 2000 ¹⁹	Laparoscopic splenectomy	500 units preoperatively	Intraoperative hypotension & bradycardia, no edema treated with 1000 units, FFP, and pRBC.
Alvarez 2000 ²⁰	Coronary artery bypass graft with cardiopulmonary bypass	1000 units 1 hour preoperativity and 1000 units 1 hour before extubation 8 hours later	
Cox and Holdcroft 1995 ²¹	Vaginal delivery	No dose specified	
Maves and Weiler 1994 ²²	Tonsillectomy	2300 units preoperatively	22 hours post-op, facial and throat swelling with difficulty swallowing - resolved within 8 hours, no mention of intervention
Martin, Carballo et al. 1993 ²³	Abdominal hysterectomy of uterine myomas	1000 units 2 hours preoperatively	
Ebert, Pritze et al. 1992 ²⁴	Caesarean section	500 units preoperatively	
Laxenaire, Audibert et al. 1990 ²⁵	1) Extensive dental surgery 2) Removal of varicose veins	1500 units 1 hour preoperatively 1500 units 1 hour preoperatively	

Abbreviations: C1-INH, C1 inhibitor; post-op, postoperatively.

Therefore, C1-INH therapy demonstrates promise as an effective, alternative perioperative prophylaxis for HAE patients who are scheduled to undergo major oropharyngeal surgery and other major and minor procedures. Further studies are recommended to evaluate safety and effectiveness and to establish optimal doses for procedure-specific perioperative management.

Mili Shum, MD
Sunit P. Jariwala, MD
David Rosenstreich, MD
Department of Medicine
Allergy/Immunology Division
Albert Einstein College of Medicine
Bronx, New York
mshum118@yahoo.com

References

- [1] Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 suppl):S51–S131.
- [2] Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol*. 2006;101:619–627.
- [3] Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000;75:349–354.
- [4] Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J Am Dent Assoc*. 2003;134:1088–1094.
- [5] Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs*. 2008;68:2561–2573.
- [6] Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363:513–522.
- [7] Bowen T. Hereditary angioedema: beyond international consensus - circa December 2010 - The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. *Allergy Asthma Clin Immunol*. 2011;7:1.
- [8] Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6:24.
- [9] Burke S, Petrov A, Johnson J, Macginnitie A. Successful use of ecallantide to treat a hereditary angioedema attack after failure of C1 inhibitor prophylaxis. *Annals of allergy, asthma & immunology: official publication of the Ann Allergy Asthma Immunol*. 2011;107:181–2.
- [10] Bernstein JA. Hereditary angioedema: a current state-of-the-art review, VIII: current status of emerging therapies. *Ann Allergy Asthma Immunol*. 2008;100:S41–6.
- [11] Czaller I, Visy B, Csuka D, Fust G, Toth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur J Obstet Gynecol Reprod Biol*. 2010;152:44–9.
- [12] Saito T, Namura O, Honma T, Hayashi J. Supplementation of C1-esterase inhibitor concentrates for a patient suffering from hereditary angioedema undergoing complex open-heart surgery. *Eur J Cardiothorac Surg*. 2010;37:975–7.

- [13] Libert N, Scherier S, Dubost C, et al. Anaesthetic management of vaginal delivery in a parturient with CI esterase deficiency. *Ann Fr Anesth Reanim*. 2009;28:375–80.
- [14] Codispote CD, Rezvani M, Bernstein JA. Successful use of CI inhibitor during mitral valve replacement surgery with cardiopulmonary bypass. *Ann Allergy Asthma Immunol*. 2008;101:220.
- [15] Nathani F, Sullivan H, Churchill D. Pregnancy and CI esterase inhibitor deficiency: a successful outcome. *Arch Gynecol Obstet*. 2006;274:381–4.
- [16] Cace N, Brusich S, Dessardo S, Ahel J. Cardiopulmonary bypass in a child with hereditary angioedema. *Pediatr Int*. 2005;47:214–6.
- [17] Maeda S, Miyawaki T, Nomura S, Yagi T, Shimada M. Management of oral surgery in patients with hereditary or acquired angioedemas: review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;96:540–3.
- [18] Alonso JM, Fas MJ. Malignant bladder tumor transurethral resection in a patient with acquired CI inhibitor deficiency. *Acta Anaesthesiol Scand*. 2002;46:740–3.
- [19] Jabbour-Khoury S, Khoury G, Soueide A, Baraka A. Laparoscopic splenectomy in a patient with acquired angioneurotic edema. *JSLs*. 2000;4:305–7.
- [20] Alvarez JM. Successful use of CI esterase inhibitor protein in a patient with hereditary angioneurotic edema requiring coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2000;119:168–71.
- [21] Cox M, Holdcroft A. Hereditary angioneurotic oedema: current management in pregnancy. *Anaesthesia*. 1995;50:547–9.
- [22] Maves KK, Weiler JM. Tonsillectomy in a patient with hereditary angioedema after prophylaxis with CI inhibitor concentrate. *Ann Allergy Asthma Immunol*. 1994;73:435–8.
- [23] Martin MJ, Carballo JC, Banos G. Anesthesia in a case of hereditary angioneurotic edema. *Rev Esp Anesthesiol Reanim*. 1993;40:29–31.
- [24] Ebert A, Pritze W, Weitzel HK. C-I esterase inhibitor deficiency as an obstetric problem: a case report. *Zentralbl Gynakol*. 1992;114:519–22.
- [25] Laxenaire MC, Audibert G, Janot C. Use of purified CI esterase inhibitor in patients with hereditary angioedema. *Anesthesiology*. 1990;72:956–7.

Allergic sensitization and symptoms, body mass index, and respiratory function in children with type 1 diabetes mellitus

The westernized and developing world is experiencing a marked increase in the prevalence of type 1 diabetes mellitus (T1DM), obesity, and allergic sensitization, affecting all age groups, including the young.¹ How these conditions may jointly affect pulmonary function is not known. Although T1DM is believed to be associated with a decreased airway reactivity,² obesity is thought to have negative implications on lung flows and volumes.³ However, when pulmonary function and bronchial reactivity have been studied objectively to prove these assumptions in children, findings have led to contradictory results.⁴ The third condition, allergic sensitization to inhaled allergens, which has been described to occur also in young patients with T1DM,⁵ may also play a confounding role in the impact of overweight/obesity on pulmonary function in patients with T1DM.

In a preliminary, cross-sectional study, we evaluated the influence of allergic sensitization and body mass index (BMI) on spirometry values in 67 consecutively enrolled, white patients (40 males and 27 females; median age, 12.99 years) with T1DM. The protocol was approved by the institutional ethical committee, and signed informed consents were obtained. T1DM was diagnosed according to positive pancreatic β -cell autoantibodies, fasting blood glucose level greater than 126 mg/dL, and insulin dependence. Diagnosis of allergic rhinitis was based on the concordance among a typical clinical history, examination of the nasal mucosa, and the demonstration of a positive skin reaction by skin prick tests.⁶ Asthma diagnosis was prompted by symptoms and confirmed by measurement of lung function to assess the presence of airflow limitation.⁷ Spirometry was performed and the results interpreted according to the European Respiratory Society guidelines.⁸

Median insulin dose in the study population was 0.90 U/kg/d, and the median hemoglobin A_{1c} level was 8.16%, reflecting good metabolic control. Median BMI standard deviation score (SDS) was 0.18 (ie, within normal limits), but 11 patients with T1DM (16.4%) were overweight (9 atopic and 6 nonatopic children) and 4 (5.9%) were obese (3 atopic and 1 nonatopic child) (Fig 1A). Sensitization to aeroallergens was shown to be present in 44 patients (65.7%) (40.8% in a control general population; $P = .006$).⁹ Current allergic rhinitis was detected in 20 patients with T1DM (29.8%) vs 16.5% in the general population ($P = .006$),⁹ whereas no T1DM patient had current asthma and the mean

spirometric parameters were within normal ranges. The median forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flows at 25% to 75% of vital capacity (FEF_{25%–75%}) values were 97.6%, 104.9%, and 115.9% of predicted, respectively (Fig 1B), whereas the median FEV₁:FVC ratio was 92 (Fig 1C). Pulmonary function parameters were similar in atopic and nonatopic patients and not affected by the presence of allergic rhinitis symptoms.

In the whole T1DM population, the BMI SDS weakly related positively with FVC ($r = 0.276$, $P = .02$), FEV₁ ($r = 0.330$, $P = .006$), and FEF_{25%–75%} ($r = 0.269$, $P = .03$) but not with the FEV₁:FVC ratio ($r = 0.125$, $P = .31$). Analyzing atopic and nonatopic T1DM patients separately, the only significant correlation detected was between BMI SDS and FEV₁ ($r = .529$, $P = .01$) in the latter subgroup.

In this preliminary study in a small, “well-controlled” T1DM population, we found a low prevalence of overweight/obesity, possibly the reflection of good adherence to the diabetic diet regimen with a correct dietary intake. We also found an unexpected positive, rather than negative, influence of BMI on lung function. This finding may be the result of not only low obesity prevalence in the study population but also of the clinical management of these patients, which included an accurate metabolic balance associated with physical activity programs. Lung function appears to decrease with increasing duration of obesity and not (yet) be impaired by an increased BMI in the youngest age,¹⁰ although the so-called respiratory function and obesity paradox has been described in other chronic conditions.¹¹

In addition, we detected a high prevalence of allergic sensitization in the T1DM population, confirming previous observations.⁵ However, despite the elevated prevalence of both allergic sensitization and current allergic rhinitis symptoms, no patient had current asthma symptoms, with spirometric parameters within the normal ranges, independently from the presence of atopy and/or rhinitis. This is in agreement with the current hypothesis that recognized T1DM as a condition associated with a decreased airway reactivity to a variety of stimuli, possibly for an initial autonomic nervous system dysfunction.¹² An ongoing follow-up study will possibly answer a still open question, that is, whether optimal management of T1DM might be a protective factor for asthma development even in patients with allergic sensitization and allergic rhinitis.

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