

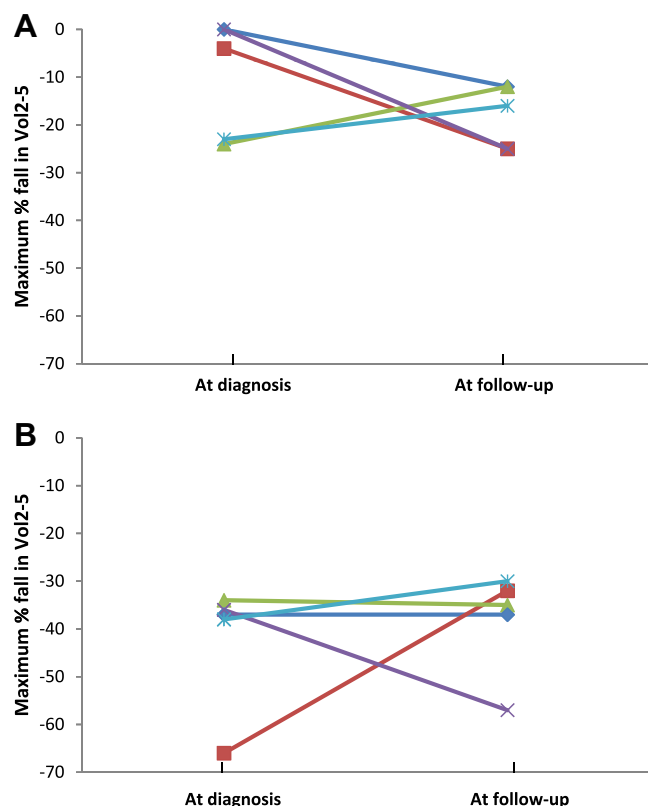


Figure 1. Individual data showing the maximum percentage fall in Vol_{2.5} from baseline values after challenge with the control (A) and the specific causal agent (B) at the time of diagnosis and at follow-up visit.

and reproducibility. However, no study has assessed its utility to reproduce the nasal response to an occupational allergen in the long term. Based on our results, we believe that it can be further recommended as a useful tool to investigate the causes of OR. Finally, this study highlights the importance of recommending reduction or avoidance of exposure to subjects with OR attributable to high-molecular-weight agents even if they no longer complain of symptoms. Also, larger studies are necessary to confirm our

observations as well as to assess the outcome of specific nasal reactivity among subjects with nonallergic OR.

Acknowledgments

The author thanks Carole Trudeau, RT, for performing the specific inhalation challenges.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.04.007>

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Estrogen-independent hereditary angioedema with normal C1 inhibitor function in a 10-year-old boy

Hereditary angioedema (HAE) is associated with an either quantitative (type I) or qualitative (type II) deficiency of the serpin C1 inhibitor (C1-INH) caused by genetic mutations within the *SERP-ING1* gene.¹ The prevalence of the disease is estimated to be less than 1 in 2,000.² More recently described is HAE with normal C1-INH function (HAEnCI-INH), frequently occurring in woman and influenced by estrogens (pregnancy, contraceptives).³ Mostly self-limited, HAE can be life-threatening, particularly if the upper airways are involved, emphasizing the need for accurate diagnosis and treatment.⁴ HAE is characterized by a subcutaneous and submucosal swelling of various organs caused by an accumulation of kinins, mainly bradykinin, onto the endothelium, leading to increased permeability of vessel and consequent localized edema.^{5,6}

HAE represents a rare but challenging differential diagnosis of acute angioedema, particularly in children, because of the similar presentation to other more frequent causes of angioedema related to histamine release. Furthermore, concomitant urticarial lesions might be present in patients with HAE, potentially leading to misdiagnosis.⁷ With this original case report of a male pediatric patient with estrogen-independent HAEnCI-INH, we emphasize that HAEnCI-INH is not limited to the predominantly described young female adult population.

A 10-year-old boy presented in our emergency department with a subacute edema of the eyelids, the right hand, the plantar region of the left foot, and the penis. He also complained of dysphagia associated with epigastric pain. All of these symptoms started 12 hours before the visit. In addition, itchy urticarial lesions on both hands and feet were reported for the previous 10 days. Medications

taken included esomeprazole for the epigastric pain and a single dose of paracetamol.

No concomitant and potentially triggering food or infectious disease could be identified. His history included atopic dermatitis in infancy as well as occasional asthma. Interestingly, 6 years before this episode, he experienced angioedema involving the face, hands, and feet while taking ibuprofen for a viral upper airway infection.

Mother and maternal aunt had childhood lip swelling episodes with spontaneous resolution, in agreement with other reports of HAEnC1-INH.^{3,8–10} No other family members were affected. No allergies were reported in the family.

On physical examination, the boy appeared anxious with a pale edema of the penis and more discrete edema of the right hand and left foot as well as a pale edema of the uvula and the anterior peritonsillar pillars, without signs of respiratory distress. The examination of the abdomen was normal.

Laboratory findings, performed during the acute episode, showed a normal serum trypsinase ($3 \mu\text{g/L}$, $N < 13$) as well as normal levels of complement C3 (0.94 g/L , $N: 0.66\text{--}1.35$) and C4 (0.14 g/L ; $N, 0.08\text{--}0.34$) and normal CH50 (115% , $N: 67\text{--}150$). C1-INH function was in the normal range (115% , $N: 67\text{--}150$). Additionally, the bradykinin metabolism has been investigated in a reference center for hereditary angioedema, and the plasma displayed an increased spontaneous activity of kinin-producing kininogenases (8.1 nmol/min/mL ; $N: 1.4\text{--}4.0$). The enzymes of kinin catabolism were within the normal range. The mutations in exon 9 of factor XII (*F12*) gene that have been associated with several cases of HAEnC1-INH have not been found in our patient.¹¹ Additional laboratory testing included a whole blood cell count, liver enzymes, thyroid function, and anti-transglutaminase antibodies; all were within normal range.

Intravenous H1 antihistamine (clemastine 0.015 mg/kg) and corticosteroid (methylprednisolone 2 mg/kg) were initially administered in the emergency room. In the absence of symptom improvement within 2 hours, we decided to give icatibant 30 mg subcutaneously. Relief of laryngeal symptoms and pharyngeal edema were reported after 30 minutes, and complete regression of skin symptoms were achieved 3 to 5 hours thereafter. Based on its known pharmacokinetics, icatibant was interpreted to be responsible for symptom remission, although we could not at this time exclude an additional effect of antihistamines and corticosteroids in symptom improvement.

In a 6-month follow-up, the boy presented 1 more attack characterized by subacute abdominal pain, slight laryngeal tightness resolving before arrival in the emergency room, and urticarial lesions on the back. Application of endovenous antihistamine (clemastine 0.015 mg/kg) and corticosteroid (methylprednisolone 2 mg/kg) did not improve symptoms. Because of the absence of severity criteria at consultation, we decided not to administer further treatments. Evolution was spontaneously favorable within approximately 12 hours. The boy was given icatibant for use at home in case of further attacks.

Based on clinical symptoms with nonpruritic pale edema in characteristic sites of bradykinin-related angioedema and the positive family history, the boy was diagnosed with HAEnC1-INH. Clinical manifestations of HAEnC1-INH are similar to those of other types of HAE.⁸ According to a recent international position paper, HAE with normal C1-INH is suspected in the presence of recurrent angioedema with both normal C1-INH function and C4 antigen level.¹² The pathogenesis of this disease is thought to be attributable to a gain of function of the kinin-producing kininogenases, reflecting activation capacity of the contact phase proenzymes including FXII. A decreased kinin catabolism, mainly attributable to decreased activity of 1 or several of the 3 major enzymes (aminopeptidase P, carboxypeptidase N, angiotensin I-converting enzyme), also might lead to HAE.¹³ Based on these findings, new

diagnostic tools, including the measurement of the kininogenase activity and levels of major bradykinin degradation enzymes are available. High activity of the kinin-forming enzymes usually develops during the periods of attacks but remains within the normal range during the interphase. The gain of function of the missense *F12* gene product may be present in less than 15% to 20% of patients affected by this disease, with no differences in clinical symptoms in this subgroup.⁹

Even though the disease is predominantly observed in women, male adults have also been described,^{8,11} presupposing an estrogen-independent expression in selected affected families.

Only a few pediatric cases of HAEnC1-INH have been published, all in female patients. In a report on 29 patients from 13 different Spanish families by Marcos et al,⁸ a 22-year-old man reported initial onset of symptoms at the age of 14 years. As far as we know, this report is the first pediatric male case of HAEnC1-INH, suggesting that this type of angioedema might also occur in pediatric population independent of sex.

As mentioned earlier, histamine-mediated angioedema of various origins remains the most frequent cause of angioedema in childhood. Its clinical characteristics are usually different, with acute onset of reddish and widespread itchy flares. A triggering factor, in particular of infectious or allergic origin, is found most of the time. With this case report, we want to emphasize that HAEnC1-INH has to be considered in a case of subacute angioedema, even in the pediatric population. Interestingly, our patient also presented intercurrent lesions of urticaria before the angioedema. Although isolated angioedema is a common clinical presentation in HAE, associated urticaria has been described. In a recent study by Giard et al, the 15 retrospectively analyzed women with angioedema while on estrogen supplementation suffered from acute or chronic urticaria associated with angioedema. Bradykinin seems to play a central role, but the exact mechanism of mast cell activation is not known. A possible hypothesis could come from the constitutive expression of mast cell B2 receptors.¹⁴ On activation by long-lasting bradykinin production, this leads to degranulation and development of urticarial lesions in association with the angioedema phenotype.

Because of the limited number of patients, no consensus for treatment, either prophylactic or during angioedema attacks, has been published for HAEnC1-INH. Treatment is mainly based on the clinical experience of addressing other forms of HAE, and isolated case reports.^{10,15}

HAEnC1-INH is still poorly understood and probably includes different physiopathologic entities with similar clinical features and laboratory findings. Further knowledge is needed for a better understanding of this disease, which was initially thought to affect only adult women. This is important for optimal medical care, particularly in the pediatric population, in which no consensus on adequate treatment is currently recommended.

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Efficacy of American College of Allergy Asthma and Immunology symposia and workshops

Many clinicians attend annual medical meetings as a source of continuing medical education (CME), yet few studies have been completed to evaluate the efficacy of this learning environment.^{1–7} The American College of Allergy Asthma and Immunology (ACAAI) is a major provider of allergy, asthma, and immunology education for health care professionals. We evaluated the learning outcomes of educational activities at the ACAAI Annual Meeting to assess their efficacy.

We evaluated 7 symposia and 6 workshops at the 2009 ACAAI Annual Meeting that addressed clinically relevant topics. A symposium is a 90-minute activity featuring didactic talks by 3 lecturers supported by 1 or 2 moderators and can accommodate hundreds of participants. A workshop is typically a 2-hour activity featuring lectures, case discussions, and hands-on demonstrations by 1 or 2 faculty and usually accommodates fewer than one hundred participants.

Participants in the symposia and workshops activities were asked to complete case-based multiple-choice questions written in the style of the American Board of Allergy and Immunology certification examination questions. These vignettes were developed by the symposia and workshop faculty and reviewed by the ACAAI CME Committee. An example question is as follows:

Ms. BC is a 39-year-old woman with longstanding severe asthma. She is on high doses of inhaled corticosteroid/long-acting beta agonist, uses prednisone bursts every 3 to 4 months, and has chronic rhinosinusitis. You are considering the addition of omalizumab. Which of the following criteria would indicate likelihood of response to omalizumab?

- Elevated IgE
- Sputum eosinophils
- Low forced expiratory volume in 1 second
- Positive radioallergen sorbent test to house dust mite

The questions were administered before the start and at the conclusion of each activity. The symposia assessments were administered by an audience response system (Turning Technologies, Youngstown, Ohio), whereas the workshop assessments were administered on paper. In addition, a 1-month post-test was

administered to workshop attendees via a secure web survey (SurveyMonkey, Palo Alto, California). Workshop participants were also surveyed on their intent to change behavior and actual change at 1 month. Statistical analysis was conducted using means, medians, proportions, paired and unpaired *t* tests, and Spearman rho correlations. Primary outcomes were change in competence, intent to change behavior, and actual behavior change at 1 month. These outcomes were selected from a validated framework for measuring medical education outcomes.⁸ Analysis was conducted using Microsoft Excel. This was an educational intervention study that was part of an ongoing quality improvement project conducted by the ACAAI and did not require institutional review board approval.

A total of 1,005 participant encounters were included. Eight hundred forty-eight learners participated in the symposia assessments and 157 in the workshop assessments. Forty-four workshop participants completed the 1-month post-activity evaluation. In the symposia activities, the mean baseline competency test score was 45% (median, 50%; standard deviation [SD], $\pm 27\%$) which increased to 61% (median, 67%; SD $\pm 27\%$) after the activity ($P < .001$) (Table 1). All 7 symposia, except 1, had statistically significant improvements ($P < .05$) when evaluated individually.

In the workshops, the mean baseline competency score was 58% (median, 67%; SD $\pm 28\%$), which increased to 71% (median, 67%; SD $\pm 24\%$) immediately after the workshop ($P < .001$). This increase was sustained at 1 month post workshop at 73% (median, 82%; SD $\pm 28\%$, $P = .0014$). Individually, 2 of the 6 workshops had statistically significant improvements ($P < .05$) immediately after the activity and at 1 month. After the workshops, 66% of the participants indicated an intent to change their behavior, and at 1 month 40% reported an actual change in their practices based on the workshop. An example of a reported practice change is when a participant reports that she is “using fractional exhaled nitric oxide more frequently” after attending a workshop on exhaled nitric oxide. The competency improvement over baseline of the intent to change group was 13% (SD $\pm 29\%$) compared with 7% (SD $\pm 22\%$) for those who did not intend to change. However, the difference was not statistically significant ($P = .376$).

This study has several limitations. This was a nonrandomized and uncontrolled study. Some participants came late and left early, leading to incomplete data collection. Assessment items written by