

Recurrent Angioedema

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Each month we present highlights from the Ask the Expert section of the American Academy of Allergy, Asthma & Immunology (AAAAI) Web site written by the Ask the Expert editors. For more questions and answers, visit www.aaaai.org/ask-the-expert.aspx.

Patient:

The patient is a 53-year-old morbidly obese woman referred to me in late 2017 for surgical clearance for bariatric surgery. The patient has a history of recurrent angioedema (AE). Current medications are amlodipine, losartan (started in 2016), enalapril, carvedilol, spironolactone, simvastatin, and metformin.

- She first noted recurrent episodes of AE in 2007. All episodes of AE have been localized and triggered by blunt trauma to the area of involvement; for example, accidental biting of lip results in obvious lip swelling (no extension to tongue or throat). Dental procedures, including cleanings, result in facial swelling; use of the glucometer results in swelling of the finger; and blood draw on the dorsum of the hand results in swelling of the hand. There has been no history of serious or life-threatening AE affecting the airway.
- On at least 2 occasions, she used an epinephrine autoinjector for facial swelling (prescribed by an allergist in 2010); although it “seemed” to help, it still took 24 hours for the AE to resolve completely, that is, the effect certainly was not immediate or obvious. Oral diphenhydramine was used as needed with uncertain benefit. The majority of the episodes have resolved over 24 hours without specific treatment.
- The patient was treated with benazepril when these episodes of AE first began in 2007; the benazepril was discontinued in 2010 and she did not start losartan until 2016. She was not treated with an angiotensin converting enzyme inhibitor

(ACE-I) or ACE receptor blocker from 2010 to 2016 and yet continued to experience recurrent episodes of AE.

- There has been a reduction in the severity of the reactions over the past 2 years during which time she has been on losartan; for example, lip swelling is less severe with accidental biting of the lip; dental cleanings no longer result in facial swelling; and the finger does not swell with the use of the glucometer. It should be noted that she reports no other symptoms when the AE occurs and specifically does not report symptoms suggestive of anaphylaxis.
- There has been no urticaria associated with the AE; no associated abdominal cramping or diarrhea; and no family history of the same.
- The patient does, however, have a history of urticaria with ingestion of specific foods: potatoes, eggplant, peppers, and tomatoes (raw or cooked). After ingestion of these foods, she describes giant urticarial lesions on arms and feet that resolve in 24 hours with diphenhydramine; she states that “in a perfect world, no hives occur if she strictly avoids these 4 foods.” All urticarial episodes are independent of the AE. She had atopic dermatitis as a child, which has resolved.
- She was first scheduled for bariatric surgery in 2010. An allergy consult was obtained for medical clearance because of the history of AE. The patient was told that the lab results were “inconclusive,” and she was advised to avoid surgery because of the history of AE. The patient is once again hoping to have the surgery, and medical clearance is being requested because of the recurrent AE (as noted, less severe in recent years, but always triggered by blunt trauma to the involved area).
- Her comorbid medical problems include hypertension, diabetes, and hypothyroidism. She has a history of multiple pulmonary emboli in 2008 associated with deep vein thromboses. She was told that she had adrenal insufficiency in her early twenties and consulted with an endocrinologist; all she remembers being told is that “one of the male hormones was elevated and was the cause of facial hair.” She has had no follow-up for this in the ensuing 30 years.
- Recent labs in this office were normal: C1 inhibitor antigen/protein = 32 mg/dL (21-39 mg/dL normal); C1 inhibitor functional activity ≥ 100% normal; C4 = 23 mg/dL (12-72 mg/dL normal); IgE = 144 kU/L. A battery of 63 food skin tests was negative.

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Questions:

1. Are there any additional laboratory studies you would recommend performing?
2. Is it safe to recommend that the patient move forward with the bariatric surgery?
3. If the cause of the AE remains undetermined and you do recommend that she could consider undergoing surgery,

would you recommend any prophylactic pretreatment or treatment to have on hand during surgery in the event she develops AE?

Response:

The description seems most consistent with a form of AE provoked by trauma. It is unclear to me whether antihistamine, epinephrine, or corticosteroid therapy is helpful as would be expected if this were a histamine-dependent form of AE. The duration of 24 hours in my experience would be more typical of histamine-dependent rather than bradykinin-dependent AE.¹ However, the trauma-associated worsening is suggestive of a bradykinin-dependent AE. I do not think that the urticaria history is related to the AE because the urticaria episodes are more limited in frequency and are not coexistent.

The normal laboratory tests exclude classic hereditary AE (HAE), but the possibility of bradykinin AE with normal C1 esterase inhibitor remains. The onset occurring after 40 years of age would not be typical because most of these cases occur in menstruating women who are younger. In addition to mutations in Factor XII of the clotting cascade (Hageman factor), there are reports of plasminogen abnormalities being associated with AE.² Of some interest, the patients with plasminogen gene abnormalities had more tongue swelling and less facial, abdominal, and extremity swelling than those with Factor XII abnormalities. This suggests a spectrum of genetic disorders with each genetic defect perhaps having clinical differences. However, plasminogen abnormalities and Factor XII mutations associated with AE are autosomal dominant, and this patient denied a family history of similar episodes. Spontaneous mutation is a possibility but the age of onset is atypical.

Some of the subjects with the plasminogen gene abnormality were treated with the bradykinin inhibitor icatibant or C1 inhibitor concentrate, and these treatments helped somewhat. There are reports of nonfamilial, nonhistaminergic AE, and some of these subjects have been treated with tranexamic acid with apparent benefit.^{3,4} There are also scattered case reports of bradykinin inhibitors being used.⁵⁻⁷

In summary, I am not convinced that your patient has bradykinin-dependent AE or HAE with normal C1 esterase inhibitor. I am reassured by the lack of laryngeal involvement, the relatively short duration of swelling, the possible response to epinephrine, and the overall reduction of episodes with time. I would discuss the issues with her and the surgeon but do not feel that surgery is contraindicated. I would not favor any pretreatment regimen because we lack evidence of what type of therapy to offer.

Your question and the above response was shared with Dr Timothy Craig, director of the allergy/immunology program at Pennsylvania State University and a major contributor to our understanding of angioedema, for his comments. His response is as follows:

I reviewed your case carefully and also the response from Dr Ledford, and I agree with many of the comments. I am concerned that your patient has histamine-induced disease because she has urticaria as well as HAE. I grant you that her history suggests that the urticaria is only associated with certain foods and the identified foods all happen to be in the same family, Solanaceae or more commonly referred to as "Nightshade." Nevertheless, I still would be suspicious that the foods are an aggravator but not cause of the "hives." I also suspect with a panel of 63 foods that at least tomato, potato, and possibly peppers were included in the skin test panel and were negative as

you noted. As Dr Ledford points out, the short duration of swelling and late age of onset of the AE are also less consistent with bradykinin-induced disease. The lack of family history also makes bradykinin disease less likely, although I admit that 25% of patients with HAE with dysfunctional or deficient C1-inhibitor do not have a family history. However, for HAE with normal C1-inhibitor, we expect a family history to be evident.⁸ Lastly, the lack of abdominal symptoms distracts me from the HAE diagnosis because most cases have a combination of skin swelling and abdominal symptoms.⁹

Before answering your questions, I would like to focus on some additional components of your patient's history. First of all, I do not believe in the recommendation that angiotensin receptor blockers (ARBs) should be avoided in a patient who had AE from ACE-I. As you know, ACE-I AE is often generated by bradykinin and the catabolism of bradykinin is not affected by ARBs. The chance of having swelling from ARBs in patients with ACE-I AE is no more likely than with any other drug.¹⁰

Despite my paragraphs above, I would always repeat laboratory tests in patients with any possibility of HAE, especially when they are having symptoms.¹¹ Most guidelines suggest 2 sets of tests, especially important in the USA because our functional assay is not as reliable as the tests used in Europe or available at National Jewish Health Advanced Diagnostic Laboratories.¹² The latter utilize a more precise and sensitive chromogenic functional assay. Lastly, her failure to respond to antihistamines at usual doses does not distract me from histamine or mast cell-induced AE. Both her AE and hives responded poorly as you note. The guidelines suggest that refractoriness to 20 mg of cetirizine twice a day suggests that exploration for bradykinin-induced disease is warranted, but I would argue that, because urticaria may require cyclosporine or omalizumab to be controlled, we should defer the diagnosis of HAE with normal C1-inhibitor until after high dose of antihistamine plus omalizumab or cyclosporin fails to control symptoms.¹³

In answer to your questions:

1. I would not do additional testing in this patient. Instead I would advance her therapy to include cetirizine 20 mg bid, and if this does not control her symptoms, I would add omalizumab. If she fails to be controlled with this regimen, I may consider further assessment for HAE with normal C1-inhibitor to include Factor XII (Hageman factor) gain of function and maybe other genetic testing.
2. I would move forward with surgery because she has metabolic disease and the benefit from the procedure outweighs the risk of AE.
3. I personally would not administer prophylaxis similar to radio-contrast reaction prevention with oral prednisone 50 mg 13 and 7 hours before the procedure and oral prednisone 50 mg and intravenous diphenhydramine 50 mg 1 hour before the procedure.¹⁴ Some clinicians would consider this relatively benign regimen to minimize chance of postoperative AE. To my knowledge, there is no evidence to support such pretreatment.

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