

Daniel visits his otolaryngologist

- Daniel visits his otolaryngologist as over the past year he has experienced recurrent swellings of his tongue, cheek and lips. This is occasionally preceded by a strange skin rash
- The following case is based on experiences from real patient cases, and has been adapted for educational purposes

Case created by:

Susanne Trainotti, Otolaryngologist, University Hospital Ulm,
Ulm, Germany



Patient history

- Daniel is consulting his otolaryngologist to discuss the tongue, cheek and lip swellings he has been experiencing
- He mentions that he also had a strange skin rash before some of these swellings
- Daniel has tried treating the swellings with antihistamines in the past, but he mentions that they were ineffective
- He is unaware of any allergies, but notes that he has never had any tests
- He suspects that he may be intolerant to lactose due to recurrent abdominal bloating
- When asked about other medical conditions, Daniel mentions that he has hypertension

1. Which of these symptoms may occur in patients with hereditary angioedema? (select all that apply)

- A. Swelling of the genitals
- B. Abdominal swelling
- C. Swelling of the face
- D. Hypertension
- E. A skin rash that is not itchy

1. Which of these symptoms may occur in patients with hereditary angioedema? (select all that apply)

- A. Swelling of the genitals**
- B. Abdominal swelling**
- C. Swelling of the face**
- D. Hypertension
- E. A skin rash that is not itchy**

Feedback

- Skin swellings of the extremities, face, genitals and trunk, as well as abdominal pain/swelling, occur in the majority of patients with HAE¹
- Many patients with HAE experience erythema marginatum, a non-pruritic rash that usually appears prior to the onset of swelling episodes. The rash may sometimes be the only symptom of an HAE attack, particularly in children²
- Hypertension is not associated with HAE. Increased vascular permeability during HAE attacks may result in hypotension in these patients, however³

Angiotensin converting enzyme (ACE) inhibitors

- When asked if he is taking any regular medication, Daniel states that he began taking the angiotensin converting enzyme (ACE) inhibitor, ramipril, 3 months ago for his hypertension
- ACE inhibitors prevent the degradation of bradykinin, leading to increased levels, which can result in bradykinin-mediated angioedema¹
- In order to determine if Daniel's swellings are induced by the ACE inhibitor he is taking, you recommend that Daniel speaks to his cardiologist for an alternative antihypertensive, such as an angiotensin II receptor blocker, beta blocker, or calcium channel blocker
- Up to 17% of patients experiencing an ACE-inhibitor mediated angioedema may also suffer from this condition when using angiotensin II receptor blockers²

2. Which of these statements regarding ACE inhibitor-mediated angioedema are correct? (select all that apply)

- A. Symptoms of ACE inhibitor-mediated angioedema may occur after years of treatment
- B. ACE inhibitor-induced angioedema occurs in more than 1:1000 users
- C. The face is the most common site of ACE inhibitor-mediated angioedema
- D. Abdominal symptoms are rare
- E. All of the above

2. Which of these statements regarding ACE inhibitor-mediated angioedema are correct? (select all that apply)

- A. Symptoms of ACE inhibitor-mediated angioedema may occur after years of treatment
- B. ACE inhibitor-induced angioedema occurs in more than 1:1000 users
- C. The face is the most common site of ACE inhibitor-mediated angioedema
- D. Abdominal symptoms are rare
- E. All of the above**

Feedback

- Reports suggest that ACE inhibitor-induced angioedema occurs in 0.1–0.7% of users¹
- ACE inhibitor-induced angioedema may occur within hours of the initial dose, or after many years of treatment²
- The face is the most common site of ACE inhibitor-mediated angioedema, and abdominal involvement is rare¹

ACE, angiotensin converting enzyme

1. Bernstein *et al.* *Int J Emerg Med.* 2017;10:15; 2. Kaufmann B. *P T.* 2013;38(3):170–172.

Skin symptoms

- Knowing that ACE inhibitors also trigger swelling attacks in patients with HAE, you want to better understand if Daniel's additional symptoms could be related to HAE
- Daniel is asked how long the swelling episodes last. He reports that they usually last 2–3 days
- When asked about the skin rash, he noted that it was not itchy. You show Daniel some photographs to better understand the skin rash and swelling he has been experiencing (see below)
- Daniel confirms that his rash looked like the picture on the left, and never like the middle picture. When seeing the image on the right, Daniel mentioned that his hand would sometimes swell up like this after handcraft at home, and one foot sometimes swells after hiking



3. Which statement is not true (select one)

- A. Wheals are edemas of the superficial skin layer
- B. Angioedema is edema in the deep skin layer
- C. The picture on the left shows urticaria – a symptom of HAE
- D. The picture on the left shows erythema marginatum – a symptom of HAE

3. Which statement is **not** true (select one)

- A. Wheals are edemas of the superficial skin layer
- B. Angioedema is edema in the deep skin layer
- C. The picture on the left shows urticaria – a symptom of HAE**
- D. The picture on the left shows erythema marginatum – a symptom of HAE

Feedback

- The image on the left does not show urticaria. This is an example of erythema marginatum, which is a prodromal sign of HAE, particularly in the pediatric population¹
- The middle image depicts urticaria. These wheals are swellings of the superficial skin layer, and often accompany mast cell-mediated angioedema that occurs as a result of allergy¹
- The image on the right is an example of angioedema – swelling of the deep skin layer. These may be a result of either mast cell- or bradykinin-mediated pathways²

A deeper dive into the patient history

- By this point, you suspect that the swelling is not mast cell-mediated
- Due to additional gastrointestinal symptoms and erythema marginatum, there is a possibility that Daniel has hereditary angioedema

4. You ask Daniel if any family members have experienced swellings, but he is not aware of symptoms among his relatives. Should hereditary angioedema still be suspected? (select one)

- A. Yes, because *de novo* mutations are responsible for ~25% of cases
- B. Yes, because HAE is an autosomal recessive disease
- C. No, because HAE is an autosomal dominant disease

4. You ask Daniel if any family members have experienced swellings, but he is not aware of symptoms among his relatives. Should hereditary angioedema still be suspected? (select one)

A. Yes, because de novo mutations are responsible for ~25% of cases

B. Yes, because HAE is an autosomal recessive disease

C. No, because HAE is an autosomal dominant disease

Feedback

- HAE is a rare autosomal dominant condition affecting an estimated 1 in 50,000 individuals. If a parent has HAE, there is a 50% chance of their offspring inheriting the disease
- However, inherited HAE accounts for only ~75% of cases. In approximately 25% of patients, a *de novo* mutation of the *SERPINC1* gene is responsible for the condition;¹ therefore, HAE should not be ruled out based on a lack of family history of the condition

Daniel experiences an acute attack

- During the consultation, Daniel develops a globus sensation, his speech gets lumpy and he is experiencing dyspnea

5. What steps should you perform in the first instance?
(select all that apply)

- A. Use transnasal endoscopy to assess the larynx
- B. Secure an intravenous line and administer corticosteroids and antihistamines
- C. Administer antifibrinolytics, since HAE is suspected
- D. Provide oxygen by a mask

5. What steps should you perform in the first instance?
(select all that apply)

A. Use transnasal endoscopy to assess the larynx

B. Secure an intravenous line and administer corticosteroids and antihistamines

C. Administer antifibrinolytics, since HAE is suspected

D. Provide oxygen by a mask

Feedback

- If there are signs of airway obstruction, including dyspnea, the laryngeal status may be assessed by transnasal endoscopy
- It is important to avoid manipulation of the mouth and tongue, in order to prevent exacerbating an angioedema attack. For reasons unknown, there are no reports of angioedema attacks of the nasal mucosa¹
- Provide oxygen by a mask, and secure an intravenous line to administer corticosteroids and antihistamines. If HAE is not yet diagnosed, or is not probable, the standard therapy for the far more common histamine-mediated angioedema should be applied first
- The use of fibrinolytics is no longer advised for on-demand treatment of acute HAE attacks²

6. Endoscopy confirms that Daniel is experiencing laryngeal edema and you consider protective intubation. He has not responded to anti-allergy medication. What are your next steps? (select all that apply)

- A. If the tongue is swollen, consider performing oropharyngeal intubation
- B. If the intubation is not successful, a coniotomy must be performed quickly
- C. After securing the airways, begin targeted HAE-specific therapy
- D. Order blood tests for C1-inhibitor function and concentration if available at your facility

6. Endoscopy confirms that Daniel is experiencing laryngeal edema and you consider protective intubation. He has not responded to anti-allergy medication. What are your next steps? (select all that apply)

A. If the tongue is swollen, consider performing oropharyngeal intubation

B. If the intubation is not successful, a coniotomy must be performed quickly

C. After securing the airways, begin targeted HAE-specific therapy

D. Order blood tests for C1-inhibitor function and concentration if available at your facility

Feedback

- Airway patency must be established
- If the tongue is swollen, the oropharyngeal pathway may be obstructed, therefore endotracheal intubation may not be possible. This procedure may also further exacerbate an HAE attack of the upper airways. Therefore, nasopharyngeal intubation should be performed.¹ For reasons unknown, there are no reports of edema of the nasal cavity²
- If intubation is unsuccessful, a coniotomy (also known as cricothyrotomy) must be performed quickly
- Once airway patency is secured, since there is a high suspicion of HAE, targeted HAE-specific therapy should be initiated. C1 esterase inhibitor (C1-INH), ecallantide, or icatibant are recommended as first-line medication for the on-demand treatment of HAE attacks³
- Blood tests for C1-INH function and concentration should be requested for diagnosis

Diagnosis

- You secure Daniel's airway via nasopharyngeal intubation
- As you strongly suspect Daniel has HAE, you begin treatment with intravenous C1-INH. His symptoms abate 1 hour following treatment
- Blood tests for C1-INH are requested, which show low concentration and function. Genetic analysis for *SERPING1* gene mutations confirm that Daniel has HAE type I
- He is referred to an HAE specialist in order to develop an appropriate treatment plan

Diagnosis	C1-INH concentration	C1-INH function	C4
HAE type I	↓	↓	↓
HAE type II	normal	↓	↓
HAE nC1	normal	normal	normal

Take-away messages

- Laryngeal attacks of HAE can be life-threatening, especially in undiagnosed patients
- There is no way of predicting whether the next attack will be laryngeal. As such, the fear of laryngeal attacks is a major cause of anxiety in patients with HAE
- An earlier, correct diagnosis is vital in order to appropriately treat and, ideally, prevent laryngeal attacks from occurring, with the aim of improving the patient's quality of life

Take-away messages

- Here is a reminder of important considerations for otolaryngologists:
 - Dig deeper into the patient's history, outside of otorhinolaryngology
 - During an acute attack, try to avoid manipulation of the mouth and throat
 - Use transnasal endoscopy to assess the laryngeal status
 - Perform transnasal intubation if the tongue is swollen, and coniotomy if unsuccessful
 - If HAE is suspected, start HAE-specific therapy as soon as possible
 - Refer patients to an HAE centre in order to confirm the diagnosis and provide optimal treatment

7. Which of the following statements are true regarding laryngeal attacks of HAE?

- A. ~50% of patients with HAE experience at least one laryngeal attack in their lifetime
- B. Laryngeal attacks can be the first symptom of HAE
- C. Before HAE-specific treatment was available, the mortality rate of patients that experienced a laryngeal attack was ~30%
- D. All of the above

7. Which of the following statements are true regarding laryngeal attacks of HAE?

- A. ~50% of patients with HAE experience at least one laryngeal attack in their lifetime
- B. Laryngeal attacks can be the first symptom of HAE
- C. Before HAE-specific treatment was available, the mortality rate of patients that experienced a laryngeal attack was ~30%
- D. All of the above**

Feedback

- Around 50% of all patients with HAE experience at least one laryngeal attack in their lifetime¹
- While uncommon, it is possible that laryngeal edema is the first symptom for patients with HAE
- Because of the risk of suffocation, laryngeal edema can be fatal if symptoms are not alleviated and/or airway patency is not quickly restored. As such, the mortality rate of laryngeal attacks before specific treatment was available was around 30%¹
- It is vital that a correct diagnosis of HAE is made early, to prevent or quickly treat laryngeal attacks