Identifying Beth’s attack triggers

- Beth is a 36-year-old female who was first diagnosed with HAE type I at 15 years of age
- Today, Beth has come to the clinic for a routine check-up, after experiencing greater HAE activity since her previous visit
- The following case is based on experiences from real patient cases, and has been adapted for educational purposes. Images do not represent real patients

Case created by:

Dr Thomas Buttgereit,
Institute of Allergology,
Charité – Universitätsmedizin Berlin,
Berlin, Germany

*Images may not represent real patients

HAE, hereditary angioedema.

Date of preparation: July 2022; EUR-BRN-0342

Patient history I

- Beth first showed symptoms of HAE when she was 10 years old, which included gyrated erythema and swelling of the lip
  - She was treated with antihistamines and systemic corticosteroids; however, her lip swelling persisted
- Over the next few years, Beth presented with additional swellings that were not responsive to treatment with antihistamines and corticosteroids, and a diagnosis remained elusive
- It is unknown whether Beth has a family history of HAE, as both parents passed away when she was young
  - However, her grandmother reports that Beth's mother had sporadic swelling during her adolescence without diagnosis

HAE, hereditary angioedema.

1. Antihistamines are considered a first-line therapy for on-demand treatment of HAE attacks?

A. True

B. False

HAE, hereditary angioedema.

1. Antihistamines are considered a first-line therapy for on-demand treatment of HAE attacks?

A. True

B. False

HAE, hereditary angioedema.

Feedback

- Antihistamines are effective in the treatment of histamine (mast-cell)-mediated angioedema
- Because HAE is bradykinin mediated rather than histamine mediated, antihistamines and corticosteroids are ineffective at resolving swellings in HAE[1]
  - Failure to respond to antihistamines, glucocorticoids, omalizumab or epinephrine is one of the characteristics that should prompt suspicion of HAE type I or II[1]
  - A rapid triage tool has recently been developed, which identified characteristics that were frequent in patients with HAE:[2]
    - Family history of HAE (71%)
    - Previous recurrent angioedema (96%)
    - Previous recurrent abdominal pain (77%)
    - Failure to respond to allergy treatments (94%)
- The recommended first-line therapies for on-demand treatment of HAE attacks in Europe are IV C1-INH or icatibant[1]

C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; IV, intravenous.

1. Maurer et al. *Allergy*. 2022;77:1961–1990; 2. Betschel et al. *J Allergy Clin Immunol Pract*. 2020;8(1):310–317.

Patient history II

- At the age of 15, Beth was diagnosed with HAE type I
  - C1-INH protein level: 0.05 mg/mL (reference range: 0.18–0.32 mg/mL)
  - C1-INH function: 40% (reference range: 70–130% of normal plasma)
  - Complement C4 level: 0.09 mg/mL (reference range: 0.16–0.38 mg/mL)
- At this time, she was experiencing up to 8 attacks per year, commonly in the gastrointestinal tract, with attack frequency increasing around exam periods
  - On two occasions she was admitted to hospital, before laboratory tests were performed, confirming her diagnosis
- Beth was prescribed 20 IU/kg IV C1-INH for the management of acute attacks, which resolved following treatment

C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; IU, international units ; IV, intravenous.

2. Approximately how many days a year are patients with HAE absent from school/work? (select one)

A. 5 days

B. 10 days

C. 20 days

D. 50 days

HAE, hereditary angioedema.

2. Approximately how many days a year are patients with HAE absent from school/work? (select one)

A. 5 days

B. 10 days

C. 20 days

D. 50 days

HAE, hereditary angioedema.

Feedback

- A 2014 study of patients with HAE conducted in Spain, Germany, and Denmark found that data from patients who were working or in school reported an estimated 20 days missing on average per year
- Patient and caregiver absenteeism increased with attack severity and frequency
- 57% of patients with attacks at least once a month indicated that HAE has hindered their career/educational advancement (41% of those with less than 1 attack per month)

HAE, hereditary angioedema.
Aygören-Pürsün et al. *Orphanet J Rare Dis.* 2014;9:99.

Patient history III

- By the time Beth was 24 years old, attack frequency had increased to around 14 abdominal attacks per year, which were preceded by erythema marginatum, and accompanied by severe pain
- She continued treating attacks on demand with IV C1-INH (20 IU/kg)
- Beth has a history of poor dental hygiene, and at the age of 32, she underwent dental surgery due to cavities

C1-INH, C1-esterase inhibitor; IU, international units; IV, intravenous.

3. Which statements are true regarding dental care in HAE? (select all that apply)

A. Oral surgery may trigger HAE attacks

B. Non-invasive oral procedures do not trigger HAE attacks

C. Short-term prophylaxis with IV pdC1-INH is recommended prior to dental procedures

D. Patients with HAE are more likely to have regular dental check-ups

E. Improving dental care may reduce the frequency of HAE attacks

HAE, hereditary angioedema; IV, intravenous; pdC1-INH, plasma-derived C1-esterase inhibitor.

3. Which statements are true regarding dental care in HAE? (select all that apply)

A. Oral surgery may trigger HAE attacks

B. Non-invasive oral procedures do not trigger HAE attacks

C. Short-term prophylaxis with IV pdC1-INH is recommended prior to dental procedures

D. Patients with HAE are more likely to have regular dental check-ups

E. Improving dental care may reduce the frequency of HAE attacks

HAE, hereditary angioedema; IV, intravenous; pdC1-INH, plasma-derived C1-esterase inhibitor.

Feedback I

- It is well recognised that dental surgery may precipitate angioedema near the site of intervention[1]
  - Local angioedema usually occurs within 48 hours following the dental procedure[1]
- There are also reports of angioedema triggered by non-invasive oral procedures, such as dental impressions[2,3]
- WAO/EAACI guidelines recommend considering short-term prophylaxis (STP) before medical, surgical, or dental procedures, as well as exposure to other angioedema attack-inducing events[1]
  - IV pdC1-INH is the recommended first-line therapy for STP[1]
  - It is believed that following tooth extraction, more than a third of HAE patients without pre-procedural prophylaxis may develop local angioedema[1]
  - There are numerous case reports of dental surgery, where pre-procedural prophylaxis with IV pdC1-INH successfully prevented HAE attacks[4,5]

EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; IV, intravenous; pdC1-INH, plasma-derived C1-esterase inhibitor; WAO, World Allergy Organization.

1. Maurer et al. *Allergy*. 2022;77:1961–1990; 2. Maeda et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;96(5):540–543; 3. Aziz and Tin. *NY State Dent J*. 2002;68(2):42–45;
4. Cinquini et al. *Case Rep Dent*. 2022; 6602411; 5. Zanichelli et al. *PLoS ONE*. 2020;15(3):e0230128.

Feedback II

- A study found that significantly fewer patients with HAE had routine dental visits within 6 months, relative to control patients[1]
  - Patients with HAE that had a >6 month interval were more likely to have experienced post-procedural attacks previously[1]
- In a recent study of patients with HAE, 59% had a moderate-to-high score for the severity of oral pathology[2]
- Infection is a common trigger for HAE attacks.[3] Since the need for dental procedures is indicative of infections of the oral cavity, improving dental care may be a useful strategy to reduce the frequency of angioedema attacks[2]

HAE, hereditary angioedema.

1. Singh et al. *J Allergy Clin Immunol Pract*. 2020;8(9):3162–3169.e5; 2. Zanichelli et al. *PLoS ONE*. 2020;15(3):e0230128; 3. Zotter et al. *Orphanet J Rare Dis*. 2014;9:44.

Discovering Beth’s attack triggers

- Following dental surgery, Beth experienced an attack in her lip, which was treated with IV C1-INH
- However, she was concerned as she required further dental surgery 3 months later, so she visited her physician for advice
  - They recommended pre-procedural prophylaxis with IV C1-INH <6 hours prior to the surgery
- The treatment successfully prevented another attack following the second surgery
- At the age of 33, Beth was prescribed treatment for hypertension

C1-INH, C1-esterase inhibitor; IV, intravenous.

1. Singh et al. *J Allergy Clin Immunol Pract*. 2020;8(9):3162–3169.e5; 2. Zanichelli et al. *PLoS ONE*. 2020;15(3):e0230128; 3. Zotter et al. *Orphanet J Rare Dis*. 2014;9:44.

4. Which of these statements are true regarding hypertension in patients with HAE (select all that apply)

A. Hypertension is a common comorbidity in patients with HAE

B. ACE inhibitors can trigger attacks in patients with HAE

C. Patients without HAE may develop angioedema as a result of ACE inhibitor use

D. All of the above

ACE, angiotensin converting enzyme; HAE, hereditary angioedema.

4. Which of these statements are true regarding hypertension in patients with HAE (select all that apply)

A. Hypertension is a common comorbidity in patients with HAE

B. ACE inhibitors can trigger attacks in patients with HAE

C. Patients without HAE may develop angioedema as a result of ACE inhibitor use

D. All of the above

ACE, angiotensin converting enzyme; HAE, hereditary angioedema.

Feedback

- Although it is not directly caused by HAE, hypertension is a common comorbidity seen in patients with HAE
  - In a recent survey of patients with HAE, 12.8% reported also having hypertension[1]
- ACE inhibitors prevent the degradation of bradykinin, leading to increased levels that can result in bradykinin-mediated angioedema[2]
  - Antihypertensive agents containing ACE inhibitors may therefore increase the frequency or precipitate HAE attacks and should therefore be strictly avoided[3]
  - Alternative hypertensives include beta blockers, or calcium channel blockers; angiotensin II receptor blockers have also been found to induce angioedema in up to 17% of users that have previously experienced angioedema when taking ACE inhibitors[4]
- Reports suggest that ACE inhibitor-induced (non-hereditary) angioedema occurs in 0.1–0.7% of users, and may occur within hours of the initial dose, or after many years of treatment[5]

ACE, angiotensin converting enzyme; HAE, hereditary angioedema; IV, intravenous; pdC1-INH, plasma-derived C1-esterase inhibitor.

1. Mendiviil et al. *Orphanet J Rare Dis.* 2021;16:94; 2. Kotis et al. *Curr Hypertens Rep.* 2018;20(7):55; 3. Maurer et al. *Allergy.* 2022;77:1961–1990; 4. Haymore et al. *Ann Allergy Asthma Immunol.* 2008;101:495–99; 5. Bernstein et al. Int J Emerg Med. 2017;10:15.

At today's visit…

- Beth (aged 36) is visiting you, her current physician, today as she has reported an increased frequency in attacks
  - She is now experiencing around 5 attacks per month
  - She is displaying poor disease control (AECT=6) and impaired quality of life (AE-QoL=83)
- After discovering that Beth is taking ACE inhibitors for her hypertension, you advise that she should stop as they may trigger HAE attacks, and instead prescribe a calcium channel blocker
- Beth describes how her lifestyle is being inhibited due to the unpredictability of attacks, and that she would like to start a family in the near future
  - She has an active lifestyle with several hobbies, including hiking and mountain biking, and a busy social life when she is not experiencing attacks
- You establish that Beth may benefit from long-term prophylaxis (LTP) to prevent attacks

ACE, angiotensin converting enzyme; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life; HAE, hereditary angioedema.

5. Which of these statements regarding long-term prophylaxis in HAE are true? (select all that apply)

A. Patients with HAE should experience at least 10 attacks per year before being offered LTP

B. LTP with attenuated androgens is the recommended first-line therapy

C. Pregnant patients should not be treated with attenuated androgens

D. LTP with HAE-specific treatments improves quality of life measures in addition to reducing attack frequency

E. Due to the availability of prophylactic therapy, complete control of HAE is becoming a realistic possibility for some patients

C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis.

5. Which of these statements regarding long-term prophylaxis in HAE are true? (select all that apply)

A. Patients with HAE should experience at least 10 attacks per year before being offered LTP

B. LTP with attenuated androgens is the recommended first-line therapy

C. Pregnant patients should not be treated with attenuated androgens

D. LTP with HAE-specific treatments improves quality of life measures in addition to reducing attack frequency

E. Due to the availability of prophylactic therapy, complete control of HAE is becoming a realistic possibility for some patients

C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis.

Feedback

- WAO/EAACI guidelines recommend that LTP should be individualized and considered in all patients with HAE type I and II. Evaluation of patients with HAE for LTP is recommended at every visit, taking disease activity, burden and control, as well as patient preference into consideration
- The recommended first-line therapies for LTP in adults with HAE are pdC1-INH, lanadelumab and berotralstat
- Attenuated androgens are recommended only as a second-line therapy for LTP, due to associated adverse effects
  - Androgens may lead to virilization of the female fetus and are, therefore, absolutely contraindicated during pregnancy

EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; LTP, long-term prophylaxis; pdC1-INH, plasma-derived C1-esterase inhibitor; WAO, World Allergy Organization.
Maurer et al. *Allergy*. 2022;77:1961–1990.

Feedback II

- In addition to reducing attack frequency, LTP with recommended first-line HAE-specific treatments has been associated with improvements in quality of life measures vs. baseline:
  - Subcutaneous C1-INH improved in overall quality of life, anxiety, depression, productivity, treatment satisfaction (TSQM) and angioedema-specific tools (AE-QoL and HAE-QoL)[1]
  - Berotralstat improved AE-QoL and TSQM scores[2]
  - Lanadelumab-treated patients demonstrated improvements in AE-QoL scores[3]
- Due to the availability of prophylactic therapy, complete control of HAE is becoming a realistic possibility for some patients. Guidelines have been updated to state that the goals of treatment are to achieve total control and to normalize patients' lives[4]

AE-QoL, Angioedema Quality of Life; EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; HAE-QoL, Hereditary Angioedema Quality of Life; LTP, long-term prophylaxis; pdC1-INH, plasma-derived C1-esterase inhibitor; TSQM, Treatment Satisfaction Questionnaire for Medication; WAO, World Allergy Organization.

1. Lumry et al. *Orphanet J Rare Dis.* 2021;16:86; 2. Farkas et al. *Clin Transl Med.* 2021;11(4):e12035; 3. Lumry et al. *Allergy.* 2021;76(4):1188–98;
4. Maurer et al. *Allergy.* 2022;77:1961–1990.

Next steps

- After discussing the potential benefits of LTP with Beth, she agrees that this treatment may be suitable for her lifestyle
- You prescribe Beth with twice-weekly SC C1-INH (60 IU/kg) for LTP, because:
  - C1-INH is the recommended LTP for treatment of pregnant patients with HAE, should Beth wish to start a family
  - She has been successfully treating attacks on demand with C1-INH IV for many years
- You schedule a follow-up appointment in 3 months to discuss the outcome of the treatment

C1-INH, C1-esterase inhibitor; IU, international units; IV, intravenous; LTP, long-term prophylaxis; SC, subcutaneous.

Key messages

- HAE should be considered when edema does not respond to antihistamines/corticosteroids
- Avoid the use of ACE inhibitors/angiotensin II receptor blockers in patients with HAE because these may worsen disease activity
- A thorough patient history is essential for understanding potential attack triggers, e.g., dental hygiene/surgery, other medications, exam stress
- The use of short-term prophylaxis with IV C1-INH should be considered before events and procedures that may induce attacks
- Consider disease-related quality of life, disease control, disease activity, and patient preference in your treatment decision making
- These factors may change over time; regular appointments should be scheduled to discuss and modify treatment options as necessary

ACE, angiotensin converting enzyme; C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; IV, intravenous.