Catherine’s experience with androgen treatment

- Catherine is a 72-year-old female from Spain
- Her first HAE symptoms occurred when she was 18 years old, but she wasn’t diagnosed with HAE type 1 until she was 62 years old
- Today, Catherine has come to the clinic for a routine check up, after switching her treatment 6 months ago
- The following case is based on experiences from real patient cases, and content and images have been adapted for educational purposes

*Images may not represent real patients

Case created by:

Professor Anna Sala-Cunill,
Allergy Section, Internal Medicine Department,
Hospital Universitari Vall d’Hebron,
Barcelona, Spain

HAE, hereditary angioedema.

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Patient history I

- Catherine is unaware if her mother, father, or other ancestral family members had HAE, but two of her three children have the condition
- She was diagnosed in 2010 with HAE type I following her son's diagnosis, when she was 62
  - Diagnostic delay = 43 years
- She has previously suffered severe and frequent angioedema attacks, which could be brought on by certain triggers

HAE, hereditary angioedema.

1. What parts of the body are most commonly affected when a patient experiences an HAE attack? (select all that apply)

A. Gastrointestinal tract

B. Brain

C. Face

D. Extremities

E. Upper respiratory tract

F. Lower respiratory tract

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Feedback

- Episodic attacks of HAE most commonly occur as asymmetric cutaneous swellings of the extremities, face, abdomen and genitals; and swellings of the gastrointestinal tract[1]
  - A prospective study found that 46% of attacks were peripheral and 33% were gastrointestinal[2]
  - Attacks in the abdomen can be painful and are often misdiagnosed as more common gastrointestinal conditions[3,4]
- Intraoral swellings, and angioedema of the brain, joints, and lower respiratory tract are rare[1]
- HAE attacks affecting the upper respiratory tract are also uncommon (~2% of swellings); however, around 50% of patients with HAE experience potentially life-threatening laryngeal swellings in their lifetime[1]

HAE, hereditary angioedema.

1. Longhurst et al. *Lancet*. 2012;379(9814):474–81; 2. Agnosti and Cicardi. *Medicine (Baltimore)*. 1992;71:206–15; 3. Maurer et al. *Allergy*. 2022; 4. Mormille et al. *Eur J Gastroenterol Hepatol*. 2021;33(6):787–93.

2. Which of these are triggers associated with HAE attacks?

A. Stress and trauma
B. Medications
C. Diet
D. Hormonal changes
E. All of the above

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Feedback

- A recent study assessed the factors causing HAE attacks via questionnaires, and found the following triggers:[1]
  - Emotion and trauma (79% and 55%, respectively) in both men and women
  - Food in 36% of patients
  - Medication in 6% of patients
    - Estrogen-containing oral contraceptive agents and estrogen hormone replacement therapy may trigger attacks[2]
- The updated international WAO/EAACI guideline for the management of HAE recommends that all patients should be educated about triggers that may induce attacks[2]
  - However, as many attacks are not prompted by triggers, excessive avoidance of suspected triggers is not recommended, in order not to limit the patient's normal life

EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; WAO, World Allergy Organisation.
1. Steiner et al. *Orphanet J Rare Dis*. 2018;13(1):90; 2. Maurer et al. *Allergy*. 2022;77(7):1961-1990.

Patient history II: Treatment

- Following her diagnosis in 2010, Catherine experienced around 3 attacks per month and was prescribed stanozolol for long-term prophylaxis (2 mg every 8 hours)
- After 3 months, her disease was more controlled and she was able to reduce her stanozolol dose to 2 mg every 48 hours
  - Catherine experienced one attack every 3–4 months which she treated on-demand with icatibant (SC). If complete resolution of the attack was not achieved with SC icatibant, Catherine also used plasma-derived C1-INH (IV)

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

3. According to the new WAO/EAACI guidelines for the management of HAE, which attacks should be considered for treatment with on-demand therapy? (select all that apply)

A. All attacks
B. Attacks affecting the upper airway
C. Attacks affecting the face
D. Gastrointestinal attacks

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Feedback

- The updated international WAO/EAACI guidelines for the management of HAE recommend that all attacks are considered for on-demand treatment and that attacks are treated as early as possible
  - Any attack affecting or potentially affecting the upper airway must be treated
  - Early treatment is associated with a shorter time to resolution and shorter attack duration
- WAO/EAACI guidelines recommend intravenous C1-INH, ecallantide* or icatibant for on-demand treatment of attacks
  - It is recommended that all patients should have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times

**Ecallantide is licensed for the use in adolescents in the US only*

C1-INH, C1-esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; WAO, World Allergy Organisation.

Maurer et al. *Allergy*. 2022;77(7):1961-1990.

Catherine continues androgen treatment

- In 2016, stanozolol was no longer available in Spain
- Catherine wished to continue with oral androgens, despite being informed of possible adverse effects, and started treatment with danazol for long-term prophylaxis (50 mg every 24 hours)
  - She did not want to receive prophylaxis with C1-INH (IV), due to her fear of IV self-administration and her perception that this mode of administration is too difficult

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

4. Individualized treatment plans for patients with HAE should be carefully developed by shared decision making?

A. True

B. False

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A. True

B. False

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Feedback

- The WAO/EAACI guideline recommends that all patients with HAE have an action plan[1]
- A patient's action plan should be individualized to the patient and take into consideration:[2]
  - Patient choice
  - Patient symptoms
  - Patient QoL
  - The treatment setting (home vs. hospital)
  - Self-administration vs. administration by healthcare professionals
  - Efficacy
  - Safety and tolerance
- Recent years have seen agreement among experts regarding the importance of shared decision making when assessing control of HAE, as it is proposed to have several benefits, including improved disease management, better outcomes, and treatment adherence[3,4]

EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; QoL, quality of life; WAO, World Allergy Organisation.

1. Maurer et al. *Allergy*. 2022;77(7):1961-1990; 2. Banerji et al. *J Asthma Allergy*. 2021;14:119-125; 3. Maurer et al. J Allergy Clin Immunol. 2021;25:S0091-6749(21)00821-6; 4. Settipane et al. *Allergy Asthma Proc*. 2020;41:S55-S60.

Adverse events

- While using danazol, Catherine's disease remained controlled
  - She experienced only one attack every 3 months
- However, she experienced adverse effects (dyslipidemia) with danazol and therefore the dose was reduced to 50 mg every 48 hours

5. What common adverse events are associated with using androgens for long-term prophylaxis in patients with HAE? (select all that apply)

A. Bronchitis

B. Depression

C. Dyslipidemia

D. Weight loss

E. Virilization

F. Headaches

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B. Depression

C. Dyslipidemia

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E. Virilization

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Feedback I

- Long-term use of androgens is associated with adverse androgenic and anabolic events[1]
  - In patients with HAE, increased treatment duration and dose correlates with increased risk of adverse events[2]
- Common androgen-related adverse events include:[2]
  - Weight gain
  - Depression
  - Menstrual irregularities
  - Myalgia
  - Virilization
  - Headaches
  - Elevations in creatine phosphokinase level, liver function test results, and serum lipid level

HAE, hereditary angioedema.

1. Maurer et al. *Allergy*. 2022;77(7):1961-1990; 2. Riedl. *Ann Allergy Asthma Immunol*. 2015;114(4):281-288.e7.

Feedback II

- As such, WAO/EAACI guidelines recommend monitoring patients using androgens every 6 months, including blood and urine sampling, and performing a liver ultrasound every year
- Androgens are contraindicated in pregnancy, and should not be prescribed to children and adolescents
- The 2021 revision and update of the WAO/EAACI guidelines recommend that androgens should only be used as a second-line prophylactic therapy

EAACI, European Academy of Allergy and Clinical Immunology; WAO, World Allergy Organisation.
Maurer et al. *Allergy*. 2022;77(7):1961-1990.

Prophylaxis without androgens

- Decreasing the danazol dose failed to improve Catherine's dyslipidemia, and the number of attacks she experienced increased to 2 attacks per month
- As Catherine is unable to self-administer IV and has poor venous access, she was recommended 60 IU/kg subcutaneous pdC1-INH for long-term prophylaxis

IU, international units; IV, intravenous; pdC1-INH, plasma-derived C1-inhibitor; SC, subcutaneous.

At today's appointment…

- Catherine is visiting the clinic for a routine check-up
- Catherine's disease is now well controlled
  - She has an AECT score of 14 (above 10 = well controlled; maximum of 16)
  - She reports that she was attack-free for the first 3 months and has only experienced one mild peripheral attack during the past 6 months, without any adverse events
- Since starting treatment with SC C1-INH:
  - Catherine has more control over her disease
  - Patient-reported questionnaires suggest that her QoL is improved
  - Her dyslipidemia has improved

AECT, angioedema control test; C1-INH, C1-inhibitor; QoL, quality of life; SC, subcutaneous.

6. In every routine appointment, which of the following factors should be assessed in patients with HAE? (select all that apply)

A. Disease activity

B. Quality of life

C. Control of the disease

D. All of the above

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Feedback[1,2]

- At every routine appointment, validated patient-reported outcome measures should be used to assess:
  - **Activity**
    - The angioedema activity score (AAS) or hereditary angioedema activity score (HAE-AS) can be used to assess disease activity and considers attack frequency
  - **Quality of life (QoL)**
    - The angioedema-QoL questionnaire (AE-QoL) or hereditary angioedema-QoL (HAE-QoL) questionnaire can be used to assess the impact of HAE on QoL
  - **Control of angioedema**
    - The angioedema control test (AECT) can used to assess disease control by evaluating symptom frequency, unpredictability of episodes, QoL impairment and efficacy of current therapy

HAE, hereditary angioedema; QoL, quality of life.

1. Bork et al. *Allergy Asthma Clin Immunol*. 2021;17(1):40. 2. Maurer et al. *Allergy*. 2022;77:1961-1990.

Take-home messages

- Patients with HAE should be well educated about triggers that may induce HAE attacks; however, excessive avoidance is not recommended in order not to limit the patient's normal life
- Possible side effects of HAE treatments should be discussed with the patient, and patients should be continually monitored for adverse events
  - Androgens, in particular, are associated with adverse events, interact with many other drugs, and are subject to numerous contraindications.
- All patients should have a treatment plan, and treatment should be individualized according to the patient's lifestyle and their preferences
- Subcutaneous C1-INH can be a highly efficacious treatment option for patients with poor venous access and those unable to self-administer IV C1-INH
  - Subcutaneous C1-INH represents a significant recent advance towards not only increased efficacy but also reduced treatment burden resulting from ease of administration

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Maurer et al. *Allergy*. 2022;77(7):1961-1990.