OVERVIEW OF HEREDITARY ANGIOEDEMA

1. What is hereditary angioedema (HAE)?

- HAE is a rare (1:10,000–1:50,000[1]), debilitating, autosomal dominant disease resulting from deficiency of functional C1 inhibitor (C1-INH) in the contact system[2-4]
- A family history is found in 75% of cases[5]
- Attacks are generally characterized by unpredictable swelling episodes of the extremities, genitalia, trunk, gastrointestinal tract, face, and larynx[3,4]
- Once an attack begins, symptoms gradually worsen over 24–36[3] hours and may persist up to 5 days[6]

2. Are there any signs that an attack may occur?

- Most patients are able to predict that an attack will occur based on prodromal symptoms[7]
- Prodromes can last up to 48 hours, and include fatigue, nausea, aching, rash, tingling, anxiety, and mood changes[7,8]

3. What triggers an attack?

- It is often the case that triggers leading to any specific attack are unknown[9]; however, some identified triggers include*
  - Emotional distress (23% of attacks in 33% of patients in a clinical trial)[9]
  - Physical trauma (5% of attacks in 12% of patients)[9]
  - Changes in estrogen levels (9% of attacks in 11% of patients)[9]
  - Other, including infection, tissue compression, certain foods, prolonged sitting or standing,[9] and dental work[3]

4. What causes HAE?

- Most often, a mutation in the C1-INH gene[10] causes a reduction in the amount of functional C1-INH in blood plasma, affecting the contact-activation pathway[3,4]
  - In type 1 HAE, patients have low levels of C1-INH[3,10]
  - In type 2 HAE, patients have normal levels of non-functional C1-INH[3,10]
- Dysregulation of plasma kallikrein activity within the kallikrein-kinin system leads to the cleavage of high-molecular-weight kininogen and excess bradykinin production, which is responsible for the signs and symptoms associated with attacks[3,11]

5. Why is HAE often overlooked?

- Rareness, heterogeneity of presentation, and symptom overlap contribute to misdiagnoses[12]
- Common misdiagnoses†: angioedema (allergic, 55.7%; nonallergic, 20.5%) and gastroenterological disorders (appendicitis, 27.0%; biliary disorder, 5.4%; gastroesophageal reflux disease, 4.9%; peptic ulcer, 3.8%)[12]

*In an observational registry study of 395 patients, 104 of whom provided trigger data.
†In an observational registry study of 633 patients, 418 of whom provided misdiagnosis data.

6. How can HAE impact day-to-day living?

- **During an attack:** pain, anxiety, inability to perform everyday activities[6,13,14]
  - Individuals may be unable to participate in activities of daily life, including work and leisure, for up to a week if an attack is untreated[6,7,13]
  - Symptoms may recur as often as every 7–14 days if untreated[5]
- Between attacks: Patients report higher rates of anxiety, stress, depression, and other emotional burdens[15]

7. What concerns do patients with HAE have?

- Long-term impacts such as hindering educational achievement and career advancement, not pursuing certain jobs, or leaving a position permanently[14]; fear of passing the disease to children[16]
- Unpredictable attacks, severe pain, disfigurement, and potentially death due to asphyxiation[3]

8. How is HAE diagnosed?

- The following tests are used to diagnose and differentiate among the different types of HAE[3,10]:
  - Complement testing
  - Functional testing
  - Genetic testing
- Once diagnosed, immediate family members should also be tested[17]

9. Who manages HAE?

- A physician knowledgeable in HAE, such as an allergist, immunologist, dermatologist, or otolaryngologist, should oversee patient care[4]
- Patient and physician should work together to develop treatment plans, keep logs of episodes and triggers, and discuss screening options for family members[4]

10. How is HAE treated?

- Attacks are *not* responsive to antihistamines, glucocorticoids, or epinephrine[17]
- Available treatments for type 1 and type 2 HAE vary by geographic region[17]
- On-demand: C1-INH treatments, plasma kallikrein inhibitor (US only), bradykinin B2 receptor antagonist; solvent detergent-treated or fresh frozen plasma if needed[17]
- Prophylaxis: attenuated androgens and C1-INH are approved therapies for short- and long-term prophylaxis,[4] though both have side effects[17] and breakthrough attacks are common[13]

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