

Carolina experiences gastrointestinal symptoms of hereditary angioedema

- Carolina, 21, has been admitted to hospital with non-bloody and non-bilious emesis, and acute right lower quadrant abdominal pain
- The following case is based on experiences from real patient cases, and has been adapted for educational purposes

Case created by:

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Patient history 1

- Carolina first attended the hospital aged 9 with recurrent abdominal pain and distension
- She underwent gastrointestinal endoscopy with biopsy, genetic investigations (HLA-DQ2 positive) and immunoglobulin A (IgA) anti-transglutaminase test (positive)

1. Which of these are common manifestations of gastrointestinal attacks of HAE? (select all that apply)

- A. Diarrhea
- B. Vomiting
- C. Increased appetite
- D. Abdominal distension
- E. Constipation
- F. Weight loss and growth retardation
- G. Abdominal pain

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Feedback 1

- The most commonly reported gastrointestinal symptom of HAE abdominal attacks is abdominal pain (up to 93% of patients)¹
- Nausea and vomiting occur in 78% of patients¹
- Diarrhea is a symptom in 65% of patients¹
- Abdominal distension has been reported in 65% of patients¹
- If the edema involves the colon, constipation can occur²
- Weight loss and growth retardation are not symptoms of HAE
- HAE gastrointestinal manifestations are transitory, and in most cases do not cause any histological damage to the gastrointestinal tract mucosa¹

2. Up to what percentage of all clinical presentations in HAE involve gastrointestinal symptoms?

A. 20%

B. 40%

C. 60%

D. 80%

E. 100%

2. Up to what percentage of all clinical presentations in HAE involve gastrointestinal symptoms?

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Feedback 2

- Gastrointestinal involvement represents up to 80% of clinical presentations of HAE

Patient history 2

- Carolina was diagnosed with celiac disease and began a gluten-free diet
- By the age of 12, despite compliance to a gluten-free diet, Carolina continued to experience recurrent colic abdominal pain
- She also started to experience a new symptom of transient episodes of edema of the skin with no urticaria or itch
- At the age of 16, she experienced severe abdominal pain in the right lower quadrant
- Carolina was given the presumed diagnosis of acute appendicitis, and underwent an appendectomy



3. What percentage of patients with undiagnosed HAE undergo unnecessary surgery?

- A. ~1%
- B. ~5%
- C. ~20%
- D. ~50%

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Feedback 3

- Studies in China, the UK, and the US report that 19–25% of patients with HAE undergo unnecessary abdominal surgery^{1,2}
- A German study also found that patients with HAE were 2.5 times more likely to undergo abdominal surgery than individuals without HAE. Longer duration of diagnostic delay was associated with a greater number of operations³

Carolina's diagnosis 1

- Following her appendectomy, Carolina's angioedema attacks continued to occur around once a week, and sometimes correlated with her period
- The attacks were not responsive to steroid therapy
- At her current hospital admission, aged 21, Carolina is experiencing non-bloody and non-bilious emesis, and acute right lower quadrant abdominal pain
- When asked whether anyone in her family experienced similar symptoms, Carolina mentioned that her mother also had recurrent abdominal aches and skin swellings, and her maternal grandfather died of dyspnea of unknown cause

Carolina's diagnosis 2

- Given her personal and family history, HAE is strongly suspected. Carolina receives treatment with C1-INH and her symptoms resolve within 1 hour
- The following tests are also ordered at her current visit, in order to confirm the diagnosis of HAE:
 - C1 esterase inhibitor (C1-INH) antigen
 - C1-INH activity assay
 - C4
 - Genetic analysis for mutation in *SERPING1*

Test results

- Carolina's test results were as follows:
- C1 esterase inhibitor (C1-INH) antigen (undetectable)
- C1-INH activity assay (11%; normal >50%)
- C4 (0.035 g/L; normal 0.1–0.4 g/L)
- Genetic analysis showed c.2T>C (p.M-22T) mutation in *SERPING1*
- These tests were also performed for the patient's mother
- Carolina was diagnosed with HAE type I, as was her mother

4. Which of these factors may be triggers for HAE attacks? (select all that apply)

- Hormonal fluctuations/estrogen
- Emotional stress
- Physical trauma/surgery
- Physical exertion
- Medication (e.g., ACE inhibitors, estrogen-based contraceptives)
- Gastrointestinal infection
- All of the above

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Feedback 4

- All of the factors listed can be triggers for HAE attacks
- In girls, the first symptoms of HAE often manifest at the beginning of puberty. A study found that oral estrogen-containing contraceptives exacerbated the symptoms of HAE in 63–80% of women; contraceptive coils may be recommended as they are well tolerated and do not worsen symptoms.¹ Progesterone-only contraception has in fact been found to reduce attack frequency in women²
- Physical trauma and surgery are known to trigger attacks. For this reason, preprocedural prophylaxis (preferably with C1-INH) is recommended before dental or surgical procedures. C1-INH should also be on hand in the event of an attack during surgery
 - Interestingly, few women have experienced HAE attacks during labor and vaginal delivery.² As such, vaginal delivery is preferred as HAE-related complications are less likely. The mechanical trauma due to surgical incision and intubation during cesarean section may trigger attacks^{3,4}
 - Endoscopic procedures present a risk of propagating an HAE attack when assessing gastrointestinal symptoms in undiagnosed patients⁵

Feedback 4

- Medications such as angiotensin converting enzyme (ACE) inhibitors and estrogen contraceptives may increase the frequency of HAE attacks and should be avoided in patients with HAE
- Psychological stress has also been reported to be a suspected precipitator of HAE attacks
- Most attacks, however, are unpredictable, and physicians are advised not to recommend excessive avoidance of all potentially stressful situations, so as not to limit the patient's normal life

Helicobacter pylori infection as an exacerbator of HAE

- Concomitant gastrointestinal disorders may influence disease severity in patients with HAE, e.g., Crohn's disease, celiac disease and ulcerative colitis¹
- *Helicobacter pylori* (*H. pylori*) infection is a potential trigger for abdominal attacks of HAE
- The proportion of patients experiencing frequent abdominal attacks was higher among patients that were infected with *H. pylori*²
- Following the eradication of *H. pylori*, attack frequency decreased substantially²
- Screening of patients with HAE for *H. pylori* infection may therefore be warranted

5. Isolated abdominal symptoms occur without visible signs of cutaneous swelling in up to 50% of HAE attacks

A. True

B. False

5. Isolated abdominal symptoms occur without visible signs of cutaneous swelling in up to 50% of HAE attacks

A. True

B. False

Feedback 5

- A study in patients with HAE reported that 49% of 521 attacks involved abdominal symptoms only

6. HAE abdominal attacks are often misdiagnosed as which of these common gastrointestinal disorders? (select all that apply)

A. Pancreatitis

B. Food allergy

C. Appendicitis

D. Inflammatory bowel syndrome

E. All of the above

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Feedback 6

- Abdominal attacks of HAE are often mistaken for more common gastrointestinal disorders, such as appendicitis, pancreatitis, food allergy, and inflammatory bowel disease
- A recent observational study in Germany found that ~50% of patients with HAE had been misdiagnosed, most commonly with appendicitis and allergy

Summary

- You refer Carolina to an HAE specialist centre to develop an optimized management plan
- Carolina's case highlights the importance of HAE awareness, in order to prevent unnecessary abdominal surgery that is common in patients with HAE
- Gastrointestinal symptoms may be present in the absence of cutaneous edema, which presents a more challenging differential diagnosis, as these symptoms are similar to those of more common diseases
- Endoscopic procedures and surgery may trigger an HAE attack in undiagnosed patients with HAE. Early diagnosis is vital, so that prophylaxis may be used prior to triggering events
- Patient personal and family history should be investigated thoroughly in patients with a history of acute, severe, medically unexplained abdominal pain
- Gastroenterologists and other physicians should consider HAE as a potential cause of unexplained abdominal pain