HAE and Gastroenterology

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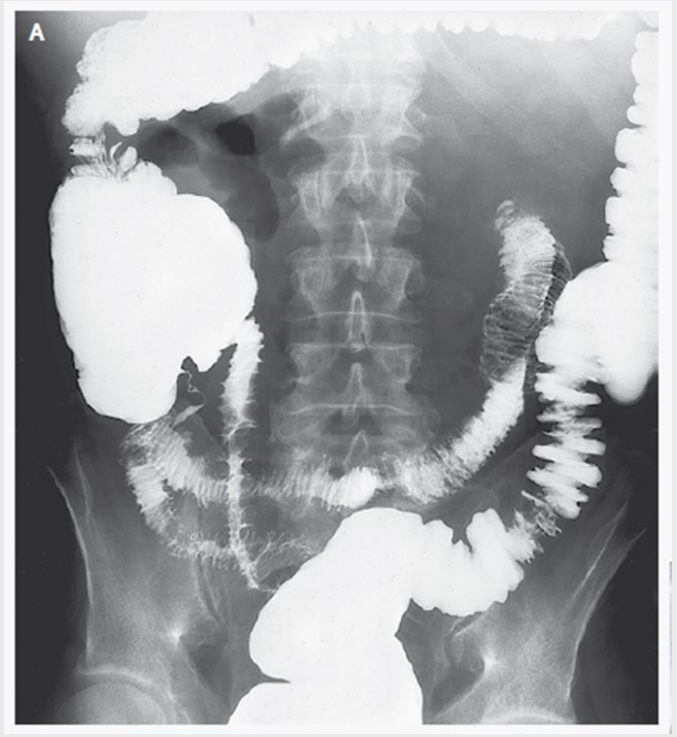


What to expect

- Introduction to gastrointestinal manifestations of HAE
- Step-by-step example of a patient case
- Treatment of HAE in gastroenterology, and the use of pre-procedure prophylaxis to control attacks
- Common misdiagnoses of gastrointestinal symptoms, and the importance of a correct diagnosis

Gastrointestinal manifestations of HAE

- **Abdominal pain** accounts for around 7–10% of all emergency department visits
- Gastrointestinal involvement represents up to **80% of clinical presentations in hereditary angioedema (HAE)**
- **Isolated abdominal symptoms** without visible signs of cutaneous swelling may occur in up to **21%** of C1 inhibitor deficient HAE (C1-INH-HAE) patients

Koruth JS, et al. *Gastrointest Endosc*. 2005:61:907

Association between gastrointestinal disorders and HAE – *Helicobacter pylori*

- Concomitant gastrointestinal disorders can influence **disease severity** in C1-INH-HAE patients, e.g. Crohn's disease, celiac disease and ulcerative colitis[1]
- ***Helicobacter pylori*** infection is a potential triggering factor of abdominal attacks
  - The frequency of acute abdominal pain is significantly higher in patients infected with *H. pylori*[2]
- Exacerbations of these abdominal attacks can be triggered by activation of the humoral immune responses, leading to the **depletion of C1-INH**
- Direct local **mucosa damage** due to cell death may lead to the activation of complement and other contact systems
- **Screening of patients with C1-INH-HAE for *H. pylori* infection** seems warranted
  - Eradication of this pathogen can lead to a marked reduction in disease severity

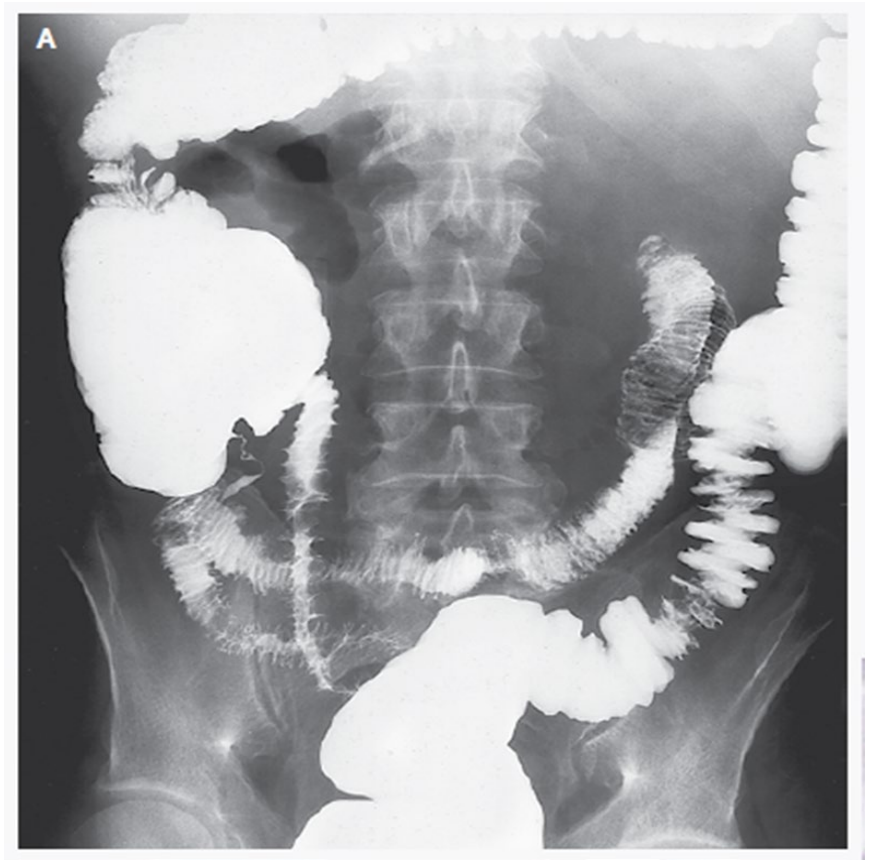
C1-INH-HAE, C1 inhibitor-deficient hereditary angioedema

1. Mormile I, et al. *Eur J Gastroenterol Hepatol.* 2020: Jul 23; 2. Visy B, et al. *Helicobacter.* 2007:12:251–257.

Gastrointestinal manifestations of HAE

Site	Clinical manifestation	Frequency (%)
Skin	Swelling and edema	97% [10]
Oropharynx	Laryngeal edema	0.9% [10]
	Tongue swelling	0.3% [10]
	Dysphagia	16% [34]
Abdomen	Nausea and vomiting	88% [34]
	Crampy and colicky abdominal pain	43–93% [12]
	Abdominal distention	72.8% [15]
	Ascites	30% [15] 80% [35]
	Diarrhea	15% [36] 65% [14]
Circulatory system	Hypovolemic shock	4.4% [15]
Less frequent presentation	Pancreatitis	Rare [13, 14, 37]
	Intussusception	Rare [13–15, 38]
	Tetany	Rare [15]
	Dysuria	Rare [39]

Patel N et al. *Case Reports in Immunology*. 2015: 925861



Bruce L. Zuraw; *N Engl J Med*. 2008; 359:1027-1036.

Unusual gastrointestinal presentation of HAE

- Ascites
- Hypovolemic shock
- Retroperitoneal angioedema
- Intussusception
- Elevated transaminase levels
- Hepatic parenchymal changes
- Pancreatitis

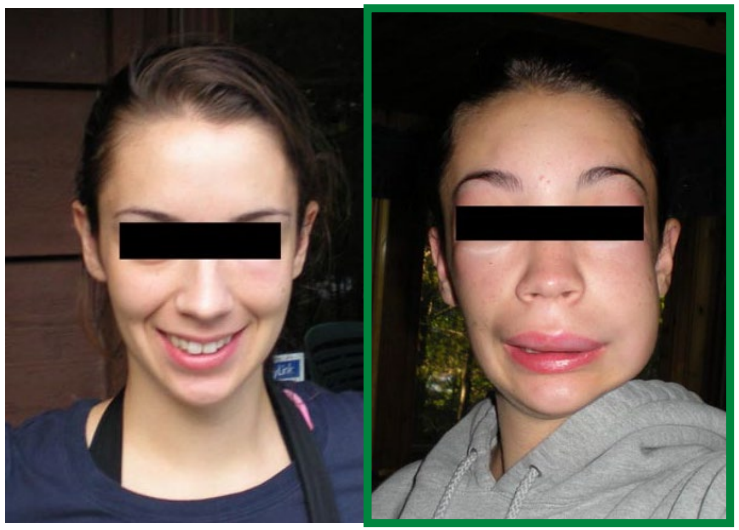
Mormile I, et al. *Eur J Gastroenterol Hepatol*. 2020: Jul 23
Image from jcomp at Freepik

Case presentation – Patient history I

- **21 year-old female**
- Admitted to the hospital for the first time at the **age of 9** with recurrent gastroenterological symptoms such as abdominal pain, distension, and diarrhoea accompanied by growth retardation
- The patient underwent:
  - Upper gastrointestinal endoscopy with biopsy
  - Genetic investigations:
    - HLA DQ2 positive result
  - IgA anti-transglutaminase screening
- The patient started a gluten-free diet with initial clinical and histological improvement

IgA, Immunoglobulin A
Image from kreativkolors at Freepik.com

Case presentation – Patient history II



By the **age of 12**, despite compliance to the gluten-free diet, she started to complain of recurrence of colic abdominal pain.

A new symptomatology emerged:

- Transient episodes of skin edema of the skin with no urticaria or itch
- Laryngeal edema, dysphonia, and dyspnoea

Images from HAEimages.com

Case presentation – Patient history III

Attack features:

- Occurred once a week
- Sometimes correlated to her period
- **Not responsive to steroid therapy**

Family history:

- The **patient's mother** also had similar recurrent abdominal aches and skin swelling
- Her maternal grandfather **died of dyspnoea** of unknown origin

Case presentation – Patient history IV

- At the **age of 16**, the patient presented to the Emergency Department with non-bloody and non-bilious emesis and acute right lower quadrant abdominal pain
  - Given the presumed diagnosis of **acute appendicitis**, she underwent an **appendicectomy**
- At the **age of 21**, she presented at our Center (Campania Referral Center for Recurrent Angioedema, University of Naples Federico II, Naples, Italy) to undergo an **allergic workup** due to suspected drug allergy to ampicillin (urticaria)

Case presentation – Diagnosis

Given her personal and family history, the following investigations were performed:

- 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*
- Laboratory and genetic tests were also performed in the patient's mother and children

She was diagnosed with C1-INH-HAE type I – as was her mother and two of her three children

C1-INH-HAE, C1 esterase inhibitor-deficient hereditary angioedema

Case presentation – Treatment

- On-demand therapy:
  - **Plasma-derived C1-INH concentrate IV** (pdhC1-INH) at a dose of 20 U/kg
- Long-term prophylaxis (LTP):
  - **Tranexamic acid** was unsuccessful and there remained a high frequency of attacks
  - Switched to **danazol** 100 mg/day, with no improvement of symptoms after 2 years of treatment
  - **pdhC1-INH IV** at a dose of 1000 IU every 4 days (self-administrated) was prescribed, with a complete resolution of symptoms and no attacks in the last 4 years

Frequency of the attacks before LTP:

2-3/week

Frequency of attack with LTP:

None

C1-INH, C1 esterase inhibitor; IV, intravenous

Berinert® 500/1500 IU (IV) is indicated for the treatment and pre-procedure prevention of acute episodes in Hereditary angioedema type I and II (HAE).

Take-home messages I

Due to its rarity and heterogeneity of manifestations, C1-INH-HAE is often poorly recognised resulting in:

- **Misdiagnoses**
- **Diagnostic delay**
- **Inadequate treatment**
- **Unnecessary procedures**
- **Increased risk of morbidity and mortality**

C1-INH-HAE, C1 esterase inhibitor deficient hereditary angioedema

Take-home messages II

- The patient underwent endoscopic procedures without prophylactic measures against laryngeal swelling because her condition was not diagnosed yet
- A significant reduction in the number of post-procedural edematous episodes has been reported in HAE patients receiving **short-term prophylaxis** before some procedures[1]
  - This includes invasive dental or medical procedures, both operative and diagnostic, with **pdhC1-INH** concentrate being the most effective drug compared to danazol or tranexamic acid

pdhC1-INH, plasma-derived C1-INH concentrate; TXA, tranexamic acid

1. Farkas H. et al. *Allergy*. 2012:67:1586-1593.

Take-home messages III

Abdominal attacks may be confused with the clinical presentation of more common gastrointestinal disorders such as:

- Appendicitis
- Cholecystitis
- Pancreatitis
- Celiac disease
- Food allergy
- Ischemic colitis
- Inflammatory bowel disease

- Although the diagnosis of HAE cannot be determined through **radiologic tests**, these investigations may be useful in excluding all other causes of abdominal pain

Conclusion

- **Personal and family anamnesis** should be accurately evaluated in patients with a long history of acute, severe, and medically unexplained abdominal pain
- Gastroenterologists and other physicians should consider **HAE as a potential cause of unexplained abdominal pain**
  - Appropriate prophylaxis and treatment will prevent needless suffering and useless surgical and medical procedures
- Complement testing for HAE should be performed in patients with **persisting abdominal symptoms** despite optimised conventional therapy
- Conversely, HAE patients unresponsive to adequate therapy should undergo a **gastrointestinal workup**

Pedrosa M, et al. *J Clin Immunol.* 2016:36:16–18.