Tara visits the pediatrician

- Tara is a 7-year-old girl presenting to her pediatrician with an intense stomach ache, vomiting and diarrhea
- She also has a swollen right hand
- Her symptoms started 12 hours ago
- This case report details the steps involved in Tara’s diagnosis of HAE
- The following case is based on experiences from real patient cases, and has been adapted for educational purposes

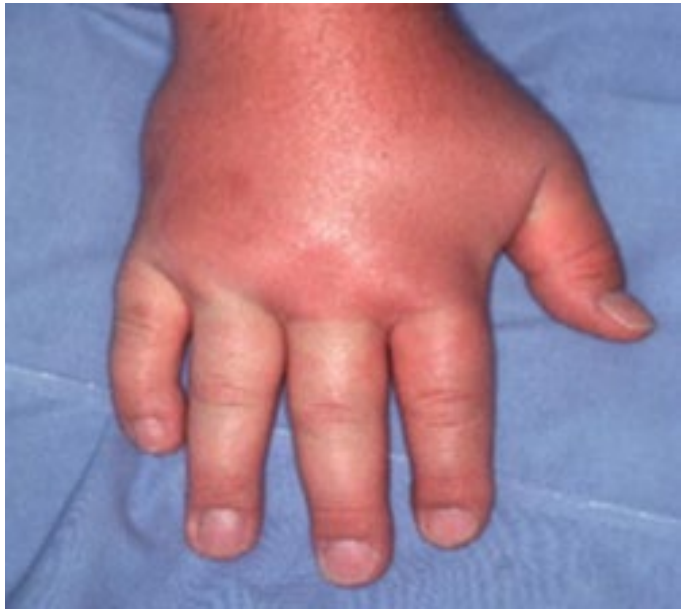
Case created by:

Dr. Christina Weber, Paediatrician, University Hospital of Zurich

Date of preparation: May 2021; EUR-BRN-0292

A deeper look into the patient history

- Her mother explains that Tara had a rash that was not itchy before the symptoms started
- The swollen hand is not pruritic and there is currently no accompanying urticaria
- The mother confirms that there is no family history of hereditary angioedema (HAE), swelling episodes or unexplained death



1. What are typical characteristics of erythema marginatum associated with HAE? (select all that apply)

A. It often spreads on the patient’s trunk and limbs

B. It often spreads on the patient’s face

C. The rash is scaly in appearance

D. The rash has a pinkish center with raised red edges

E. The rash can appear in rings or irregular shapes

F. The rash is itchy and painful

1. What are typical characteristics of erythema marginatum associated with HAE? (select all that apply)

A. It often spreads on the patient's trunk and limbs

B. It often spreads on the patient's face

C. The rash is scaly in appearance

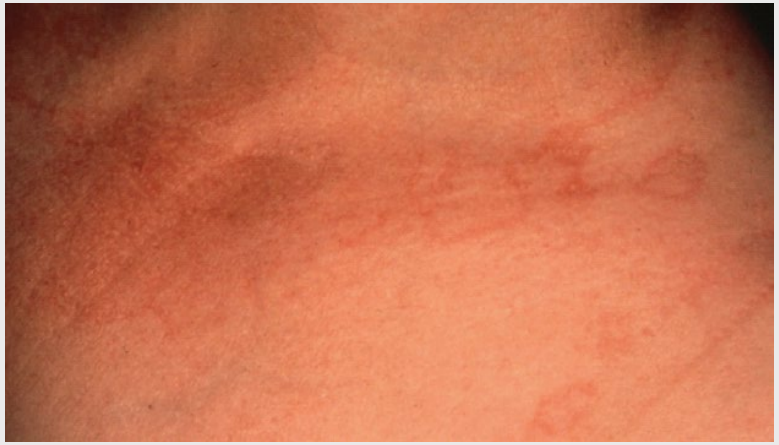
D. The rash has a pinkish center with raised red edges

E. The rash can appear in rings or irregular shapes

F. The rash is itchy and painful

Feedback

- Typically, erythema marginatum spreads on the trunk or limbs of the patient and does not usually appear on the face[1]
- The rash can appear almost pattern-like with round or irregular shapes with wavy margins, and is usually not itchy or painful[2]
- The rash usually has a pinkish center with raised borders that are usually darker in colour[2]
- An erythema marginatum rash can persist for a few hours to months at a time[1]



Used with kind permission from Mike Frank

1. Starr *et al*. *J Allergy Clin Immunol*. 1974;53(6):352–355; 2. Farkas *et al*. *Acta Derm Venereol*. 2001;81(5):376–7.

2. What step should you take next to treat Tara?

A. Administration of oral antihistamines and oral cortisone, and abdominal ultrasound

B. Administration of antibiotics

C. Take blood for further investigation

2. What step should you take next to treat Tara?

A. Administration of oral antihistamines and oral cortisone, and abdominal ultrasound

B. Administration of antibiotics

C. Take blood for further investigation

Feedback

- The swelling appears to be an angioedema; these are most frequently mast cell-mediated
- The patient's history is not suggestive of HAE at this point – there is no personal or family history of swelling or HAE
- Although mast cell-mediated angioedema is commonly associated with urticaria, it is possible for mast cell-mediated angioedema to occur in the absence of urticaria
- Mast cell-mediated angioedema is treated on demand with antihistamines, corticosteroids and adrenaline/epinephrine, if necessary
- If symptoms persist despite this treatment, HAE should be considered
- Abdominal ultrasound should be performed to investigate the cause of Tara's abdominal pain
  - Abdominal pain and swelling are also symptoms of HAE

Maurer *et al. Allergy. 2018*;73:1575–1596.

Differential diagnosis I

- Tara was treated with antihistamines and corticosteroids
- Her symptoms persisted
- An abdominal ultrasound was performed, which revealed swelling of the gut
- The physician suspects HAE

3. Which medication(s) could be used to treat Tara’s current symptoms? (select all that apply)

A. Intravenous plasma-derived C1-INH

B. Intravenous recombinant C1-INH

C. Subcutaneous lanadelumab

D. Subcutaneous icatibant

E. Attenuated androgens

F. Subcutaneous plasma-derived C1-INH

C1-INH, C1-esterase inhibitor

3. Which medication(s) could be used to treat Tara's current symptoms? (select all that apply)

A. Intravenous plasma-derived C1-INH

B. Intravenous recombinant C1-INH

C. Subcutaneous lanadelumab

D. Subcutaneous icatibant

E. Attenuated androgens

F. Subcutaneous plasma-derived C1-INH

C1-INH, C1-esterase inhibitor

Feedback

- Intravenous plasma-derived C1-INH is indicated for treatment of acute HAE attacks in children (from birth or above 2 years, depending on manufacturer)
- Recombinant C1-INH is indicated for treatment of acute HAE attacks in children above 2 years old
- Subcutaneous icatibant is licensed for treatment of acute attacks in children above 2 years old
- The use of androgen therapy is not recommended as a first-line therapy for children with HAE, due to potential interference with natural growth and maturation processes[1]
- Subcutaneous plasma-derived C1-INH and lanadelumab are licensed for use in children above the age of 12, for long-term prophylaxis from attacks

C1-INH, C1-esterase inhibitor

1. Maurer *et al. Allergy*. 2018;73(8):1575–1596.

Differential diagnosis II

- Tara was treated with intravenous plasma-derived C1-INH
  - Her symptoms resolved within 2 hours
- Blood tests were performed for C4, C1-INH concentration and C1-INH function
  - C1-INH concentration = Normal
  - C1-INH function = Low
  - C4 concentration = Low

C1-INH, C1-esterase inhibitor

4. What type of HAE does Tara have?

A. HAE Type 1

B. HAE Type 2

C. HAE with normal C1-INH

C1-INH, C1-esterase inhibitor

4. What type of HAE does Tara have?

A. HAE Type 1

B. HAE Type 2

C. HAE with normal C1-INH

C1-INH, C1-esterase inhibitor

Feedback

- Type I HAE is characterised by a reduced concentration and function of C1-INH, due to mutations in the *SERPING1* gene
  - This type accounts for around 85% of HAE cases[1]
- Type II HAE occurs when there is a normal or even increased plasma concentration of C1-INH, but its function is reduced[1]
- C4 plasma concentration is low in both Type I and Type II HAE
- An additional type of HAE has also been described where both C1-INH concentration and function are normal[2]
  - HAE with normal C1-INH (HAE-nC1) is bradykinin-related, caused by mutations in genes other than *SERPING1*, such as FXII, ANGPT1, PLG and KNG[3]
  - It predominantly affects women – high estrogen levels can trigger attacks in HAE-nC1[4]
- Reference values of C1-INH are laboratory-dependent

C1-INH, C1-esterase inhibitor

1. Maurer *et al. Allergy*. 2018;73:1575–1596; 2. Bork *et al. Allergy Asthma Clin Immunol.* 2010;6(1):15;
3. Veronez *et al. J Allergy Clin Immunol Pract*. 2021; S2213–2198(21)00312–3; 4. Magerl *et al. Immunol Allergy Clin North Am*. 2017;37(3):571–584.

5. Which of these statements about HAE are true? (select all that apply)

A. Approximately 50% of all HAE cases are inherited

B. HAE is an autosomal dominant disease. Consequently there is a 50% probability of a child inheriting HAE from a parent with the disease

C. The prevalence of HAE is believed to be approximately 1:50,000

D. There is only one known mutation in the *SERPING1* gene that causes HAE

E. Approximately 20% of HAE cases occur through spontaneous genetic mutations

5. Which of these statements about HAE are true? (select all that apply)

A. Approximately 50% of all HAE cases are inherited

B. HAE is an autosomal dominant disease. Consequently there is a 50% probability of a child inheriting HAE from a parent with the disease

C. The prevalence of HAE is believed to be approximately 1:50,000

D. There is only one known mutation in the *SERPING1* gene that causes HAE

E. Approximately 20% of HAE cases occur through spontaneous genetic mutations

Feedback

- ~75% of HAE cases are inherited, while ~25% arise from spontaneous *de novo* mutations[1]
- HAE is an autosomal dominant disease
  - If one parent has the affected gene, there is a 50% probability that their child will also have the disease[1]
- The prevalence of HAE is approximately 1:50,000[2]
- Over 450 mutations in the *SERPING1* gene are known to be associated with C1-INH-deficient HAE, and account for 95% of HAE cases[3]
- Mutations in other genes for plasminogen, angiopoietin 1 and factor XII are associated with HAE not related to C1-INH[3]

C1-INH, C1-esterase inhibitor

1. Cicardi *et al. Allergy.* 2014;69:602–616; 2. Lumry *et al. Allergy Asthma Proc.* 2020;1;41(Suppl 1):S08–S13; 3. Banday *et al. Genes Dis.* 2019;7(1):75–83.

Summary

- Tara's case describes the initial diagnosis of HAE in a pediatric patient with no family history of the disease
- Her lack of response to anti-allergy treatment suggested that Tara's symptoms were not mast cell-mediated; tests for HAE were appropriate
- Increased awareness of HAE in pediatrics is of utmost importance as the first symptoms of HAE usually occur in the first or second decade of life; yet many patients aren't diagnosed until 10 years (range 1–41 years) later[1]
- An early diagnosis of HAE allows Tara to receive appropriate care and optimisation of treatment at an early age, which may dramatically improve her quality of life

1. Wais-Knöcker *et al. Praxis*. 2010;99(19):1135–1141.