Frieda’s long journey to a correct diagnosis

- Frieda, 65, attends an angioedema specialist centre
- She has read an article about hereditary angioedema in the lay press
- She has realized that she has experienced many of the symptoms described in the article

Case created by:

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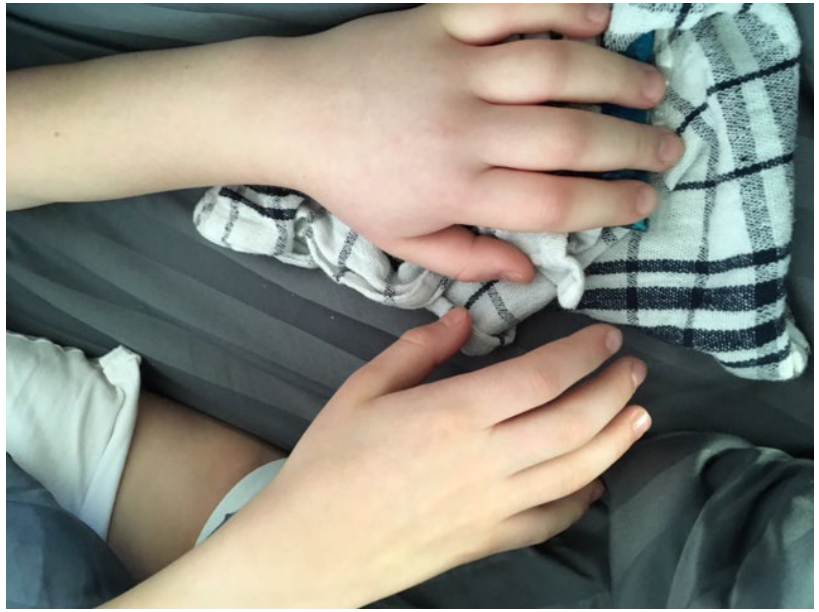
Patient history 1

- From the age of 7, Frieda experienced skin swelling once a month
- She experienced severe abdominal pain twice a year, with each episode lasting up to 7 days
- It was suggested that allergies and insect bites were the cause of her symptoms



1. What factors could help delineate allergy-mediated angioedema from bradykinin-mediated angioedema? (select all that apply)

A. Bradykinin-mediated angioedema is frequently accompanied by wheals

B. A family history of swellings is indicative of histamine-mediated angioedema

C. Failure to respond to antihistamines and corticosteroids may indicate bradykinin-mediated angioedema

D. Mast cell-mediated angioedema is often pruritic, whereas bradykinin-mediated angioedema is usually not

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Feedback

- Bradykinin-mediated angioedema does usually not occur with wheals or pruritus; however, mast cell-mediated angioedema is frequently accompanied by wheals, which are often pruritic[1]
- A family history of swellings is indicative of bradykinin-mediated hereditary angioedema[2]
- Mast cell-mediated angioedema is abated following the use of antihistamines, corticosteroids and epinephrine. If this treatment is unsuccessful, this indicates that the angioedema may be bradykinin-mediated[2]

1. Misra et al. Indian J Anasth. 2016;60(8):534–541; 2. Betschel et al. J Allergy Clin Immunol Pract. 2020;8(1):310–317.

Patient history 2

- When several allergy test results came back negative, Frieda was diagnosed as a ‘sensitive child’
- When she was 12 years old, she experienced severe abdominal pain, and was suspected to have appendicitis
- Frieda underwent an appendectomy; however, her symptoms persisted
- She was prescribed painkillers
- Frieda continued to deal with her painful abdominal attacks with the painkillers she’d been prescribed
- Many years later, after becoming a mother, Frieda’s daughter began showing similar symptoms to her, and Frieda recalled that her father always had stomach complaints

2. Which of these statements regarding HAE are true? (Select all that apply)

A. As HAE is an autosomal dominant disease, there is a 50% probability of a child inheriting HAE from a parent with the disease

B. 50% of all HAE cases are inherited

C. There are over 450 known mutations that cause HAE

D. Approximately 25% of HAE cases occur through spontaneous genetic mutations

E. The prevalence of HAE is believed to be approximately 1:5000

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Feedback

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

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

3. What percentage of patients with hereditary angioedema undergo unnecessary surgery?

A. ~5%

B. ~20%

C. ~50%

D. ~80%

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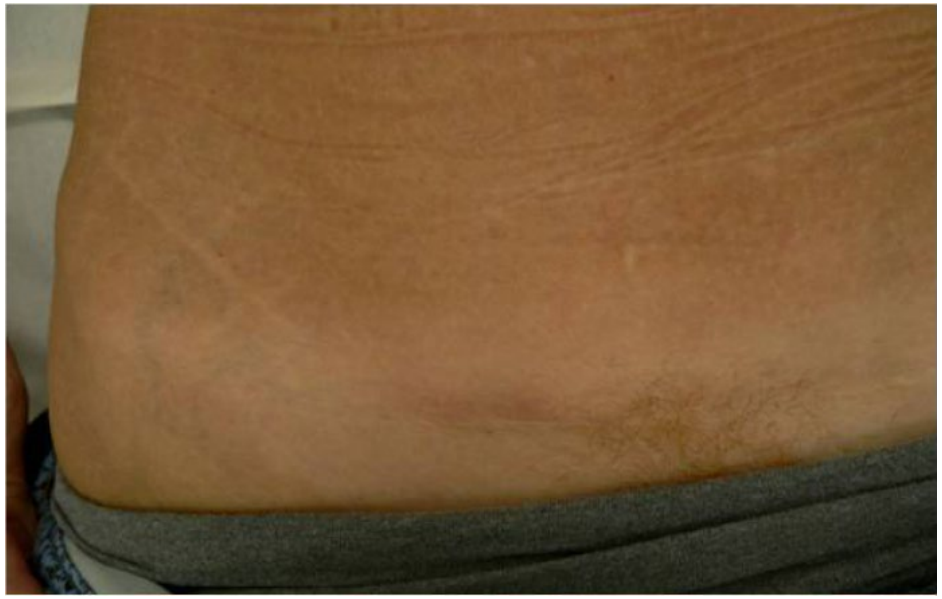
Feedback

- 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 operations[3]

1. Cao et al. Allergy Asthma Proc. 2021;42(2):131–135; 2. Patel et al. Case Reports in Immunology. 2015; Article 9925861; 3. Hahn et al. JDDG. 2018;16:1443–1449.

Patient history 3

- Frieda’s abdominal pain persisted, and as a result she underwent a hysterectomy at 38 years old
- However, despite the surgery, Frieda’s abdominal pain persisted
- After coming to terms, over decades, with the 'wait and see' approach and the use of painkillers to treat her abdominal pain, Frieda has just recently read an article in the lay press about HAE
- She feels that the description of the disease matches her symptoms, and this is what has driven her to visit your angioedema specialist centre



Diagnosis

- After detailing her personal and family history, you suspect that Frieda may indeed have HAE, and send a blood sample for testing
  - C1-INH concentration was normal
  - C1-INH function was low
  - C4 concentration was low
- Frieda was diagnosed with HAE type II

4. How could Frieda be treated? (Select all that apply)

A. On-demand treatment with icatibant or C1-INH
B. Long-term prophylaxis with androgens
C. On-demand treatment with corticosteroids and antihistamines
D. Long-term prophylaxis with C1-INH or lanadelumab

4. How could Frieda be treated? (Select all that apply)

A. **On-demand treatment with icatibant or C1-INH**

B. Long-term prophylaxis with androgens

C. On-demand treatment with corticosteroids and antihistamines

D. **Long-term prophylaxis with C1-INH or lanadelumab**

Feedback

- Subcutaneous icatibant is licensed for the treatment of HAE attacks in adults and children above 2 years old[1]
- Intravenous plasma-derived or recombinant C1-INH is indicated for treatment of acute attacks in adults and children (from birth or aged 2+, depending on manufacturer)[2,3]
- Androgen therapy has traditionally been used for long-term prophylaxis from HAE attacks; however, guidelines now do not recommend this treatment as a first-line therapy. Guidelines recommend that it is not used for the on-demand treatment of attacks, but may be used as a second-line treatment for short- or long-term prophylaxis when C1-INH is unavailable[4]
- Intravenous plasma-derived C1-INH, depending on the manufacturer, is licensed for long-term prophylaxis from HAE attacks in adults and children (aged ≥6 years).[5] Subcutaneous plasma-derived C1-INH and lanadelumab are licensed for use in adults and children ≥12 years for long-term prophylaxis from attacks[6,7]
- Corticosteroids and antihistamines are effective treatments for mast cell-mediated angioedema, therefore would not be effective in this instance, since HAE is bradykinin-mediated

1. Icatibant SmPC: https://www.ema.europa.eu/en/documents/product-information/firazyr-epar-product-information_en.pdf;
2. Intravenous plasma-derived C1-INH SmPC: https://www.ema.europa.eu/en/documents/product-information/cinryze-epar-product-information_en.pdf;
3. Recombinant C1-INH SmPC: https://www.ema.europa.eu/en/documents/product-information/ruconest-epar-product-information_en.pdf; 4. Maurer et al. Allergy. 2018;73(8):1575–1596.
5. Intravenous plasma-derived C1-INH SmPC: https://www.ema.europa.eu/en/documents/product-information/cinryze-epar-product-information_en.pdf;
6. Subcutaneous plasma-derived C1-INH SmPC: https://mri.cts-mrp.eu/Human/Downloads/DE_H_0481_004_FinalPI_2of3.pdf;
7. Lanadelumab SmPC: https://www.ema.europa.eu/en/documents/product-information/takhzyro-epar-product-information_en.pdf

Summary

- Frieda's case is an example of how HAE may be misdiagnosed for many years before a correct diagnosis is made, due to symptoms that are similar to more common illnesses
- A recent German study reported that 49.4% of participating patients with HAE were misdiagnosed – appendicitis and allergy were the most frequent misdiagnoses[1]
- Median diagnostic delay in this study was 15 years[1], although another European study reported improvement over time, and a lower median (2 years for patients with a family history; 5.6 years for those with no family history)[2]
- In the 50 years prior to her diagnosis, Frieda consulted Pediatricians, Allergists/Dermatologists, Gastroenterologists, Otolaryngologists, Emergency Room and Surgeons
- She underwent multiple unnecessary abdominal surgeries

  – Unnecessary surgeries have been reported in ~20% of patients with HAE[3,4]
- Increased awareness and collaboration by multiple medical specialties is vital in order to prevent prolonged pain and stress caused by misdiagnosis of this disease, since effective treatment is available

1. Magerl et al. Orphanet J Rare Dis. 2020;15, 221; 2. Zanichelli et al. Clin Transl Allergy. 2018;8:42; 3. Cao et al. Allergy Asthma Proc. 2021;42(2):131–135;
4. Patel et al. Case Reports in Immunology. 2015; Article 9925861.