Hereditary angioedema (HAE) in the paediatric patient

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What to expect

- Introduction HAE symptoms in paediatric patients
- Step-by-step examples of patient cases
- HAE treatment options in paediatrics
- Triggers for HAE attacks
- The importance of collaboration with HAE experts

Why is HAE relevant to paediatricians?

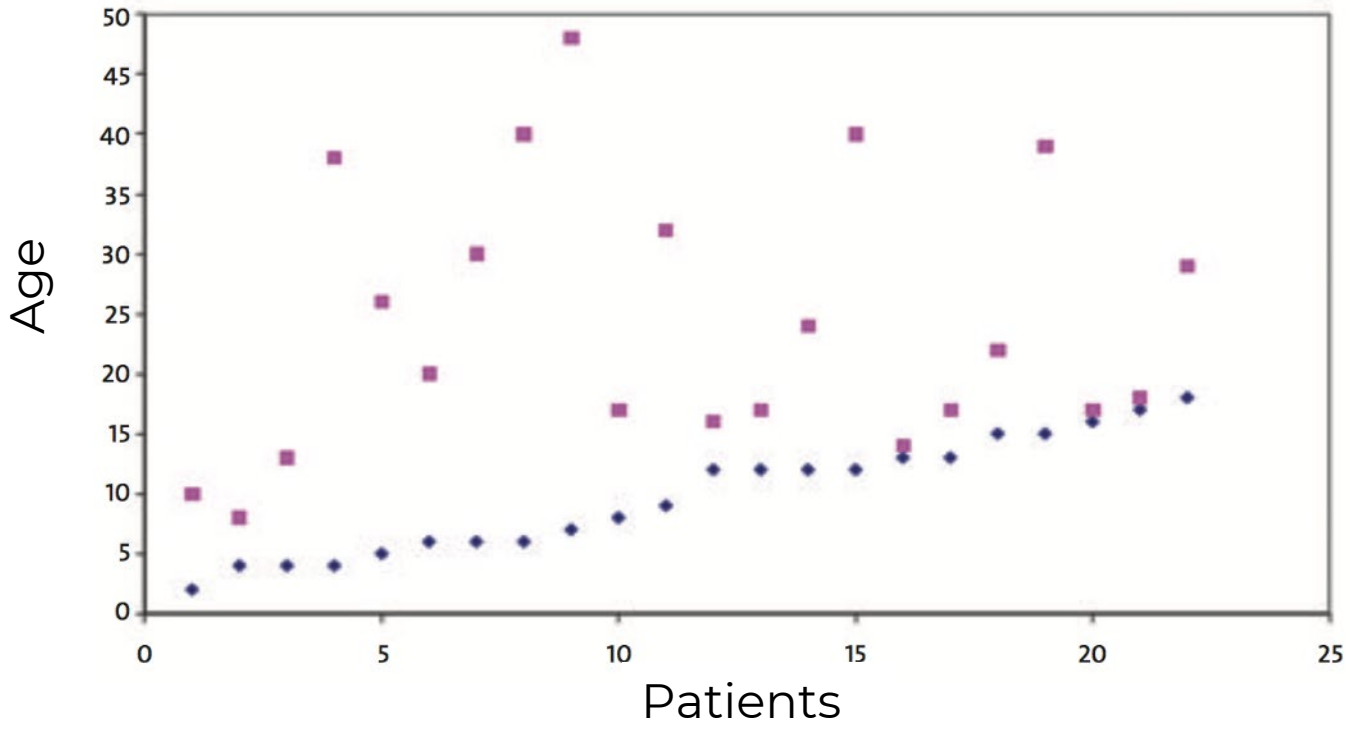
- Onset of first symptoms are very variable but mostly in the first or second decade of life
  -  USA: Half of all patients experience symptoms before the age of **6 years**[1]
  -  Hungary: **6.6 years** (4–11 years)[2]
  -  Denmark: **9.5 years**[3]
  -  Spain: **12.5 years**; asymptomatic individuals included[4]
  -  Germany: **11 years**; 90% before the age of 20 years[5]
- Always look for asymptomatic individuals in the family who may also have HAE

The diagnosis should be made as early as possible to ensure optimal management and treatment of symptoms

1. Donaldson VH and Rosen FS. *Pediatrics.* 1966; 37(6):1017–1027; 2. Farkas H, et al. *Allergy Asthma Clin Immunol.* 2010;6(1):18; 3. Bygum A, et al. *Allergy.* 2011;66(1):76–84; 4. Roche O, et al. *Ann Allergy Asthma Immunol.* 2005;94(4):498–503; 5. Bork K, et al. *Am J Med.* 2006;119(3):267–274

HAE diagnostic delay

- In a study of 22 patients without family history, the median delay before diagnosis was 10 years (range 1–41 years)[1]



Age of first manifestation

Age at diagnosis

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

Patient case 1 – History

- 3 day-old girl
- Developed a profound erythema marginatum
- Positive family history for HAE
- Was tested for C1-INH deficiency
  - Function = 13% (normal >68%)
  - Concentration = 4.7 mg/dL (normal 15.4–35.6 mg/dL)

Which type of HAE – I or II?

C1-INH, C1 esterase inhibitor

Martinez-Saguer I. and Farkas H. *Pediatrics,* 2016; 137(2)e20152411

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HAE Type I

Which type of HAE – I or II?

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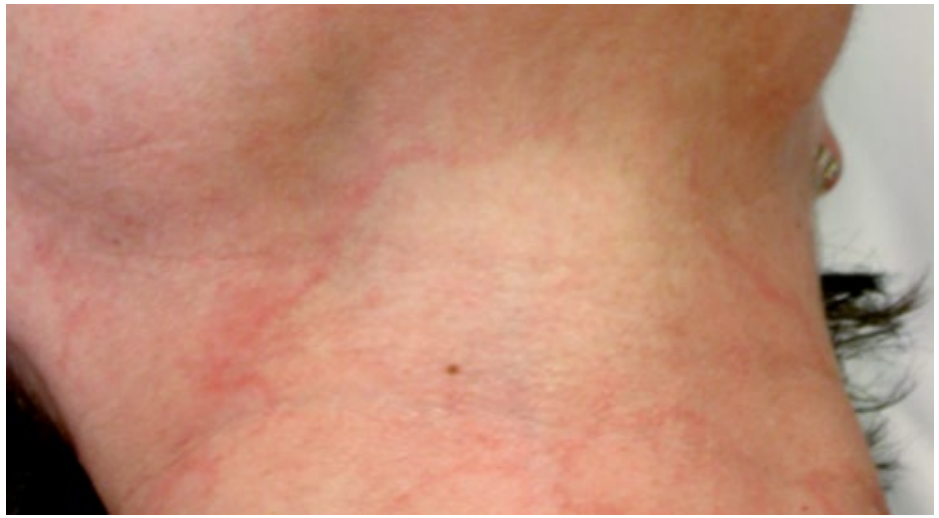
Martinez-Saguer I. and Farkas H. *Pediatrics,* 2016; 137(2)e20152411

Prodromal symptoms

- Pruritus, nausea, fatigue, malaise
- Erythema marginatum
  - Non-pitting, nonpruritic, serpiginous rash
  - First described by Osler in 1888
  - Can manifest hours to days before the onset of an attack
  - **Occurs in 42–58% of paediatric patients with HAE**



Farkas H, et al. *Acta Derm Venerol*. 2001;81(5):376–377; Bygum A. *Br J Dermatol.* 2009;161(5):1153–1158; Kjaer L and Bygum A. *Pediatr Dermatol.* 2013;30:94–96

Patient case 1 - Treatment

- Sonography: minimal edema around the liver, free abdominal fluid
- Tested negative for viral infection
- Asymptomatic: not treated

Martinez-Saguer I. and Farkas H. *Pediatrics*, 2016; 137(2)e20152411

Patient case 1 – 4 weeks later

- New outbreak of erythema marginatum
- Abdomen bulged and painful
- Sonography: ovarian cyst and free fluid in the abdomen
- 250 IU human C1-INH (weight 4 kg) IV within 30 minutes
- Relief in 7 h

C1-INH, C1 esterase inhibitor; IV, intravenous
Martinez-Saguer I. and Farkas H. *Pediatrics*, 2016; 137(2)e20152411

Patient case 1 – Between 5 weeks and 18 months

- >20 episodes of erythema marginatum
- No other symptoms
- Supplied with C1-INH for administration in case of attack

C1-INH, C1 esterase inhibitor
Martinez-Saguer I. and Farkas H. *Pediatrics*, 2016; 137(2)e20152411

Treatment options in paediatrics

On-demand		Pre-procedural prophylaxis	Long-term prophylaxis		
IV	**SC**	**IV**	**Oral**	**IV**	**SC**
Plasma-derived C1-INH Recombinant C1-INH (EU and Switzerland)	Icatibant	Plasma-derived C1-INH	Tranexamic acid (Good safety profile but not very effective[1])	Plasma-derived C1-INH	Plasma-derived C1-INH (>12 years) Lanadelumab (>12 years)

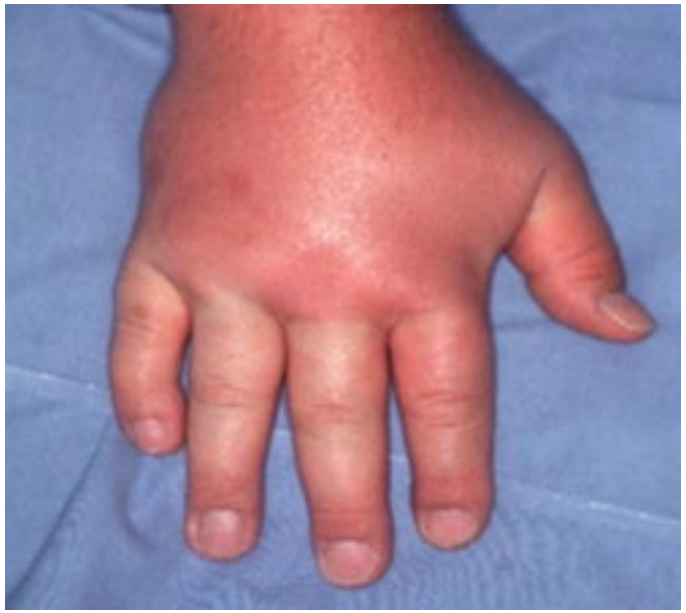
Attenuated androgens must not be used for HAE in children and adolescents due to side effects

C1-INH, C1 esterase inhibitor; IV, intravenous; SC, subcutaneous

1. Longhurst and Zinser. *Immunol Allergy Clin North Am*. 2017; 37(3):557–570

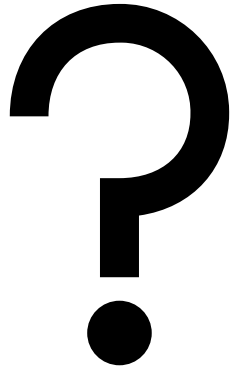
Patient case 2 – History

- 7 year-old girl
- Intense belly ache, vomiting and diarrhoea
- Swollen right hand
- Skin rash before the symptoms started
- Symptoms started 12 hours ago
- Not itchy
- Family history negative for HAE, swelling episodes or unclear death



Next step?

1. Administration of oral antihistamines and oral cortisone, and abdominal ultrasound
2. Administration of intravenous C1-INH
3. Take blood for further investigation



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C1-INH, C1 esterase inhibitor

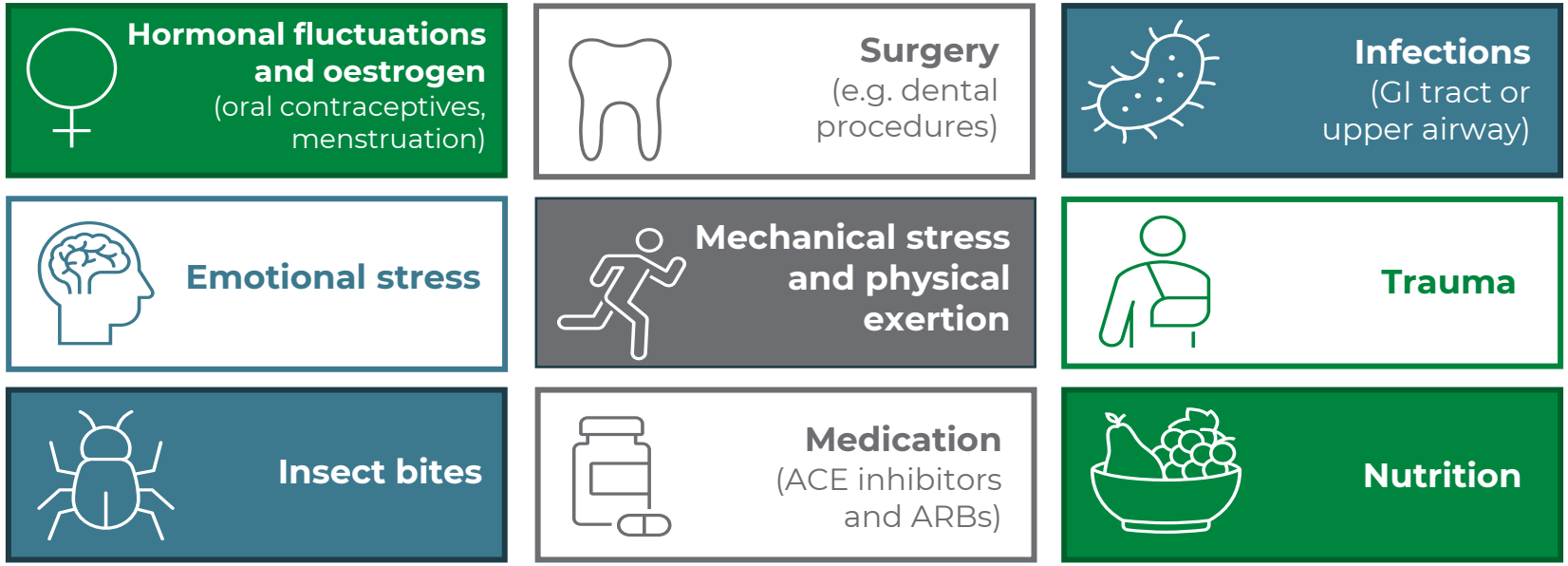
Patient case 2 – Differential diagnosis

- The patient did not respond to antihistamines or corticosteroids
- Abdominal ultrasound revealed swelling of the gut
- Patient treated with on-demand intravenous C1-INH (or FFP)
- Symptoms resolved within 2 hours
- Blood tests performed for C4, C1-INH concentration and function
  - Tests indicative of Type I HAE

C1-INH, C1 esterase inhibitor; FFP, fresh frozen plasma

Triggers for HAE attacks

- Most attacks are spontaneous without a contributing factor; however some triggering events have been linked to HAE attacks, which may be more difficult to detect in young children
- These triggers should be avoided or minimised in diagnosed patients
- Parents and teachers should be educated in how to identify and treat a potential HAE attack



ACE, angiotensin converting enzyme; ARB = angiotensin II receptor blocker; GI, gastrointestinal

Maurer M, et al. *Allergy*. 2018;73(8):1575-96.

Puberty in girls with HAE

- In girls, the first symptoms of HAE often manifest when puberty begins[1]
- **Hormonal contraception**
  - In 63–80% of women, the symptoms of HAE are exacerbated by contraceptive pills that contain oestrogen[1]
  - Contraceptive coils that are placed directly into the uterus are often well tolerated and do not worsen symptoms[1]
  - Progestin administration can act as a prophylactic strategy: total or partial improvement was seen in 82% of female patients with HAE who were administered progestin-only contraceptive medication[2]

1. Bouillet. *Allergy Asthma Clin Immunol.* 2010;6(1):17; 2. Saule et al. *Clin Exp Allergy.* 2013;43(4):475–482

Collaboration between paediatrician and HAE experts

- Parents commonly visit paediatrician first for any symptoms in their child prior to diagnosis
  - Recognition of the disease symptoms and timely diagnosis is important, and is commonly made by the paediatrician or emergency doctor
- **For prompt and effective treatment of attacks and successful management of the disease, there must be a good collaboration with HAE centres**
- Recommendations for prophylaxis:
  - Avoid triggers
  - Short-term prophylaxis before events that may trigger an attack e.g. dental surgery
- On-demand acute treatment should be made available for all children diagnosed with HAE

Frank MM et al. *Pediatrics.* 2016; 138(5):e20160575

Take-home message for paediatricians

- Patient history is important
- Think of HAE if there is a family history
- Think of HAE if there are symptoms and antihistamines and corticosteroids are not having effect
- Plasma diagnostics are needed for diagnosis
- There is good treatment available – early diagnosis is essential for optimising management and treatment of the disease

Thank you for your attention

Questions?