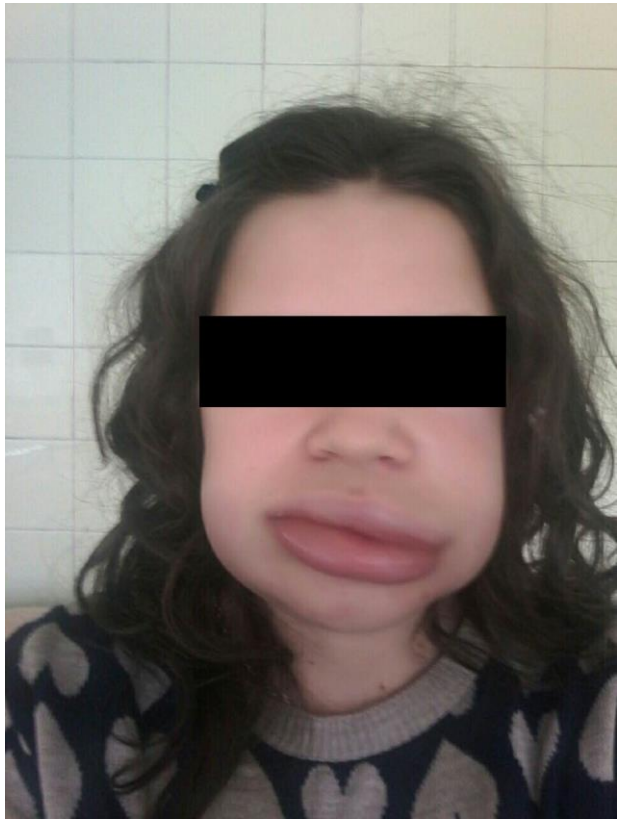
Innovative therapeutic approach of Hereditary Angioedema

Prof Dr Vesna Grivcheva – Panovska
University Clinic of Dermatology
School of Medicine
University St. Cyril and Methodius
Skopje, Macedonia

- Hereditary Angioedema (HAE) is a result of a mutation in the C1-INH gene and transfers as an autosomal dominant characteristic. The gene for C1-INH (SERPING1) is mapped on 11q12-q13.1.



- Around 300 different genetic HAE mutations have been described and a rate of around 25% spontaneous mutations.
  The two types of HAE connected to the function of C1-INH are type I (85%) and type II (15%)

- HAE type I is caused by mutations found throughout the gene and result in truncated or misfolded protein. The secretion of this protein is inefficient resulting with low antigen and functional plasma levels of normal C1-INH protein.
  Even though it is present in one normal allele, less than 50% of the functional C1-INH level is present.

- One possible explanation is that the normal C1-INH protein is downregulated which is supported by the finding of decreased levels of C1-INH mRNA in patients with HAE. Taking into consideration that C1 inhibitor bonds to the protein it deactivates and the complex is removed from the circulation, this could also be a reason for the low levels of C1 inhibitor.
- Half of the normal level of C1-INH is considered sufficient to prevent an angioedema attack.

- C1INH is single-chain plasma glycoprotein with a molecular mass of 73,650 belonging to the super-family of serine protease inhibitors in plasma.
  C1INH is the only known inhibitor of activated plasma subcomponents C1s and C1r of the complementary component 1 of the complementary cascade classical pathway.

- Furthermore, C1INH inhibits the Manan-associated serine protease 2 (MASP2) of the lectin pathway of the complement. Additionally, it is the main inhibitor of the activated factor XII, factor XI and kallikrein of the plasma contact system.

The treatment of Hereditary Angioedema is changing rapidly in the past years, thanks to advances in the production of HAE-specific medications.

MANAGEMENT

Some of the agents used for treatment of acute HAE attacks are as follows:

- C1-INH concentrate: Berinert – approved by US Food and Drug Administration (FDA) in September 2009 for treatment of acute abdominal and facial attacks of angioedema in adolescent and adult patients with HAE; in January 2012 it was approved for treatment of laryngeal angioedema as well;

MANAGEMENT

- In July 2014 FDA approved the recombinant human C1-INH (rhC1-INH) Ruconest for treatment of acute HAE attacks in adolescents and adults
- Recombinant human C1INH is a purified derivative from rabbit milk which expresses the gene that encodes the synthesis of C1INH. The amino acid sequence of the recombinant form is identical to the human C1INH.

MANAGEMENT

- rhC1INH was primarily developed for treatment of acute angioedema attacks in patients with HAE due to C1INH activity deficiency.
- The rhC1INH inhibitory potential of target proteases C1s, kallikrein, factor XIa and factor XIIa is highly comparable to the endogenous human C1 esterase inhibitory potential in vitro.

MANAGEMENT

- Additional data of the efficacy are obtained by multiple analysis of primary efficacy sensitivity end point, as well as the results of secondary and explorative efficacy.

MANAGEMENT

- Kallikrein inhibitor: during HAE attacks the unregulated activity of plasma kallikrein results in excessive production of bradykinin leading to oedema; Ecallantide (Kalbitor) is a recombinant agent which is a potent, selective, reversible kallikrein inhibitor; FDA approved Ecallantide in December 2009 for treatment of acute HAE attacks in patients aged 16 and older

MANAGEMENT

- Sellective bradykinin B2 receptor antagonist: Icatibant (Firazyr) was approved by FDA in 2011 for treatment of acute HAE attacks in adults

PROPHYLAXIS

- The medical advisory board of HAEi has recommended that patients freely chose their preferred therapy. The prophylactic treatment includes attenuated androgens and C1 inhibitor product Cinryze.

PROPHYLAXIS

- In case androgene therapy is used, the dose should be minimized, balancing the disease intensity and minimizing the side effects. Most frequently used medication is Danazol, but all attenuated androgens are useful. The usual daily recommended dose is 200 mg maximum.

PROPHYLAXIS

- The nano-filtrated C1-INH concentrate Cinryze was approved for HAE prophylaxis by FDA in 2008. There have been reports about its efficacy in acute attacks as well.

- The education of medical professionals, HAE patients, their families and caregivers as well are crucial for the successful treatment of this rare disease.

- The HAE consensus guidelines recommend that all patients should have access to on-demand treatment for acute attacks.

- According to the new patient oriented guidelines, at least 2 on-demand treatments should be available since patients often have heterogeneous responses to different medications.

AIMS FOR THE FUTURE

- Improvement of the existing medications
- Research of less invasive modalities of application such as peroral, implantable devices and biodegradable devices
- Precision and individualized medicine approaches