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GENERAL

Hereditary Angioedema (HAE)

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What is Hereditary Angioedema (HAE)?

Hereditary angioedema is a disorder that occurs due to malfunctioned or depleted C1-INH i.e. C1 esterase Inhibitor gene. It is an uncommon Autosomal Dominant disorder. It is a subset of non-allergic angioedema.

Mechanism of HAE

The pathogenic mechanism of HAE is regulated by bradykinin. C1-INH is moderator of the complement and Contact mechanisms. The contact system gets triggered if C1-INH is malfunctioned or suboptimal. This results in uninterrupted production of kallikrein, an enzyme which can cleave peptide bonds into proteins. In consequence of this, unregulated proteolysis of bradykinin and kininogen is there, which ultimately results in enhanced vascular permeability causing edema.

Types of HAE

Hereditary Angioedema is categorized into three types:

1. Type I HAE

2. Type II HAE

3. Type III HAE

Type I HAE

? Inadequacy of C1-INH gene.

? 80-85% of total cases are of Type I.

? Mutation of SERPING 1 gene which transcribe the C1- inhibitor protein.

? A range of mutations takes place in gene encoding region.

? Aberrant or curtailed C1-inhibitor protein is present, thus reduced circulating levels.

Type II HAE

? Malfunctioned C1-INH gene is produced. Patient reflects normal levels.

? 15-20% of total cases are of Type II.

? Mutation of SERPING 1 gene, predominantly a missense mutation in exon 8.

Type III HAE

? Identified as Estrogen-dependent HAE as it is highly correlated with elevated estrogen level.

? Prevalent in Female patients and worsened in case of pregnancy or user of hormonal-contraceptive.

? High level of estrogen aligns with elevated levels of factor XII a, which further raise bradykinin levels.

Clinical Judgement:

? Periodic cutaneous or submucosal angioedema coexisted with abdominal discomfort.

? The cutaneous angioedema is patchy and irregular.

? Visceral angioedema, which involve visceral organs is primary factor in identifying the disease.

? Laryngeal edema is a fatal visceral complication, patient with HAE may encounter.

? Children are often non-symptomatic, but symptoms are reported before the age of 20 years.

? HAE attack is may be triggered by trauma, medical procedures, stress, hormonal contraceptives and ACE inhibitors.

? During diagnosis, patient should not have high body temperature or fever nor the patient should have urticaria or hives.

Laboratory Tests

? Insufficiency/ deficiency of C1 esterase inhibitor, which may result in high levels of bradykinin.

? Low levels of C1-INH due to deficit SERPING 1 gene.

? Monitoring C4 level and D-dimer level in case of acute attack.

? Genetic testing

Treatment and Management

Acute Treatment

? Swelling diminishes in 3-5 days in the absence of treatment.

? In case of laryngeal edema, prompt action is required.

? Primary objective of acute treatment is to restrain rapid progression.

? The treatment should be begun as early as within 6 hrs. for more favorable outcomes.

? The Acute treatment offers plasma-derived C1-INH (pdC1-INH), recombinant human C1-INH (rhC1-INH), ecallantide and icatibant.

? These drugs are impactful within 60 mins, and comfort is seen beneath 2 hrs.

? Incase of unavailability of above drugs FFP i.e. Fresh Frozen Plasma containing C1-INH is used. (Although NOT RECOMMENDED, as level of evidence is low)

? Intravenous (IV) options include pdC1-INH and rhC1-INH.

? Histamines, antihistamines, epinephrine and glucocorticoids are ineffective.

Short-term Prophylaxis

? Trauma and stress due to some medical procedures (such as; oral surgery, endoscopy, endotracheal intubation) may stimulate acute attacks.

? IV or SC dose immediately before the procedure or a 5 days course of androgens before the procedure and followed by 2-3 days may work.

? Tranexamic acid (TXA) is an antifibrinolytic medication, primarily used during surgeries to prevent blood loss. A case report demonstrates that it may treat ACE inhibitor-induced angioedema.

Long-term Prophylaxis

? Prevalence and criticality of attacks, its consequences, healthcare availability, coexisting conditions are considered before deciding whether it is long term prophylaxis or not.

? Monoclonal plasma kallikrein inhibitors are primary treatment options.

? Antifibrinolytics or anabolic agents are considered as alternative treatments or secondary therapies.

? Androgens should be avoided in pregnant patients as well as in pre-adult teens.

? In case of pregnant ladies and children tranexamic acid is considered as alternative agent.

Competing interests

The authors declare that they have no competing interests.

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