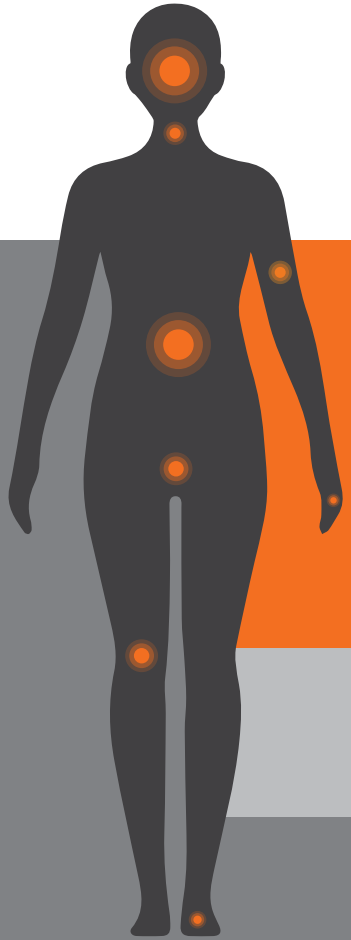

HAESI
HEREDITARY ANGIOEDEMA SOCIETY OF INDIA

EDUCATIONAL BOOKLET ON

Hereditary Angioedema

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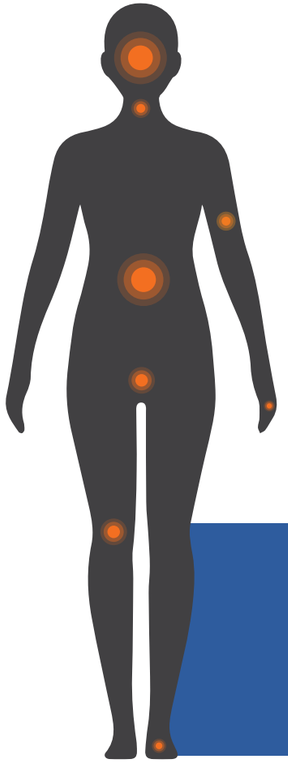
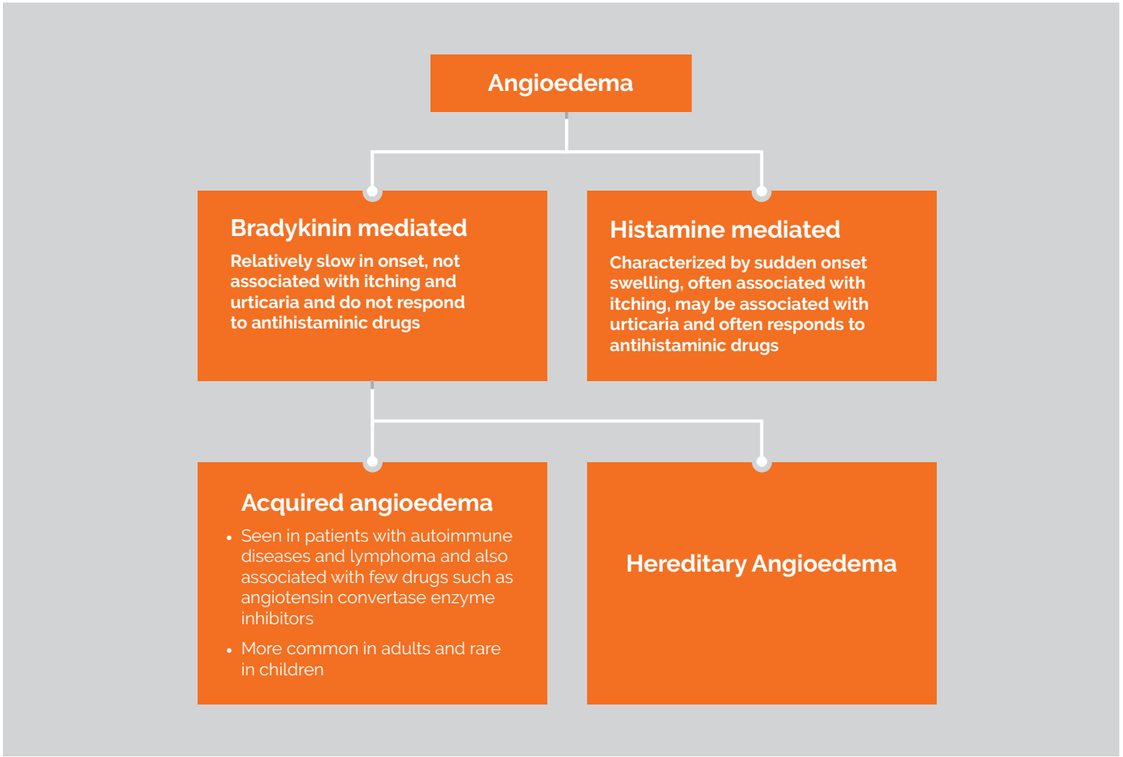


INTRODUCTION

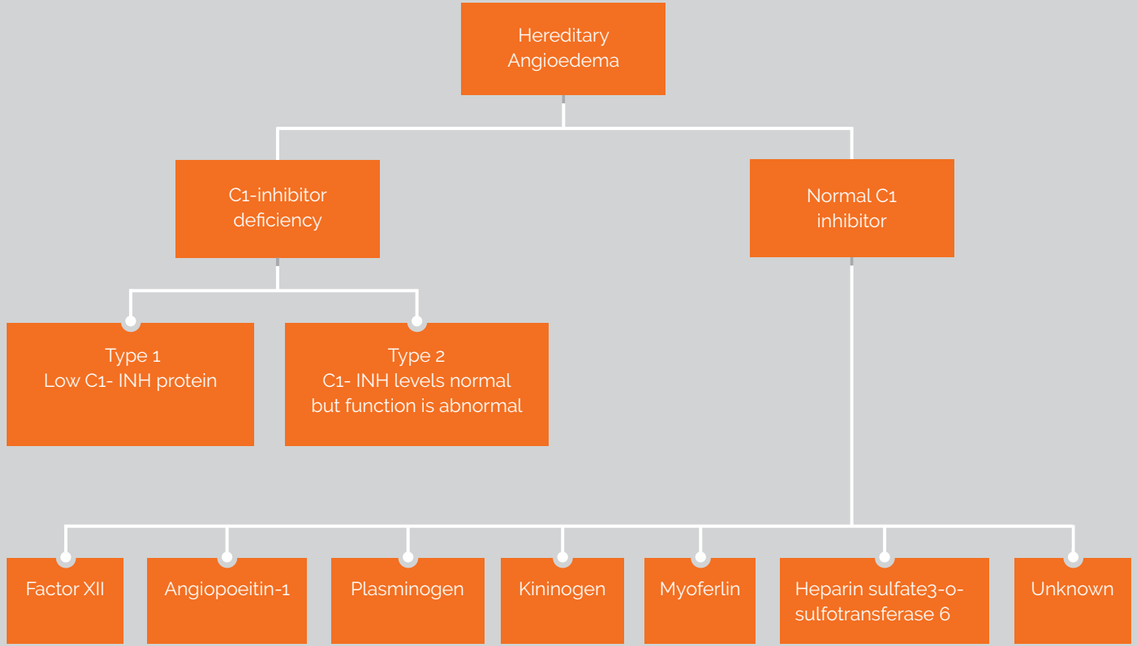
- Angioedema is characterized by swelling of subcutaneous and/or submucosal tissue because of increased vascular permeability.
- Angioedema may be broadly categorized into histamine and bradykinin mediated.
- Most cases of hereditary angioedema (HAE) have onset in childhood.
- HAE is an uncommon, potentially life-threatening disease and has an autosomal dominant mode of inheritance.
- HAE is characterized by episodes of subcutaneous and/or submucosal swelling typically affecting extremities, face, genitals, airway and gastrointestinal mucosa.

DO YOU KNOW?

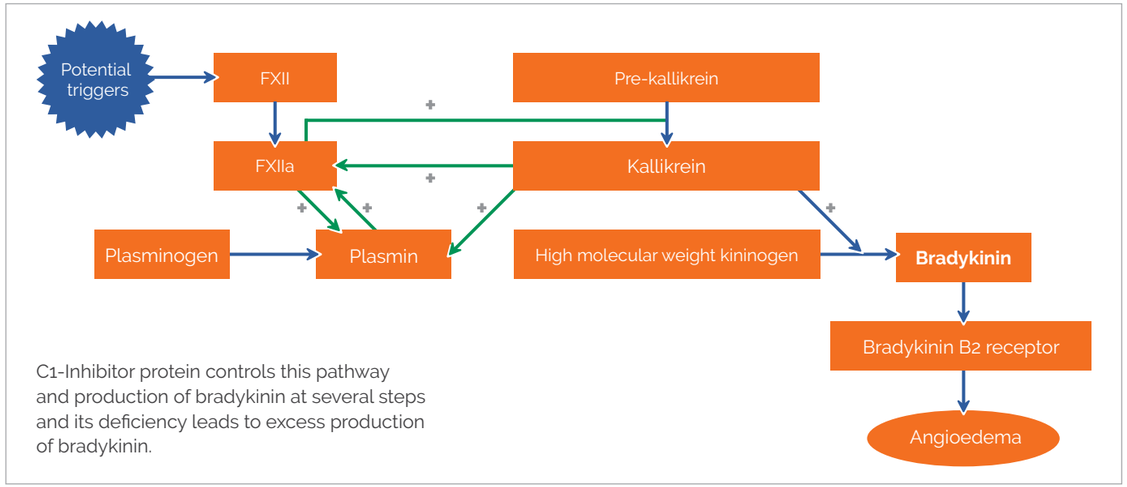
- The global prevalence of HAE is 1:10,000 to 1:50,000
- It is expected that there are more than 50,000 patients with HAE in India at present
- HAE is grossly underrecognized in India. Because of lack of awareness, most patients with HAE remain undiagnosed and untreated.



CLASSIFICATION OF HAE



PATHOPHYSIOLOGY OF C1-INH HAE



The figure shows the pathway for production of bradykinin and angioedema. C1-INH protein is an inhibitor of various complement proteases, contact system proteases (FXIIa, Plasma kallikrein), intrinsic coagulation pathway and fibrinolytic pathway.

Deficiency of C1-INH protein or impaired function of C1-INH protein as is seen in patients with type 1 and type 2 HAE respectively, leads to uncontrolled activation of FXII, plasma kallikrein and over production of bradykinin. Bradykinin stimulates its receptor to cause vasodilatation, increased vascular permeability and angioedema.

Pathophysiology of normal C1-INH-HAE is more complex. There is role of bradykinin and vascular endothelium in mediating episodes of angioedema in these patients.

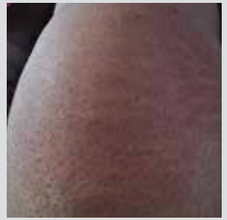
CLINICAL MANIFESTATIONS OF HAE

- Non-pitting, non-urticarial, non-pruritic subcutaneous and/or submucosal swelling.
- Typically lasts for 3 - 5 days.
- Most attacks are spontaneous. A trigger such as physical or mental trauma, infection, surgical or dental procedure may be identified in few cases.
- Limbs, face, eyes, lips and genitals are the most commonly involved sites.
- Bowel wall edema may lead to abdominal pain, vomiting and occasionally diarrhoea.
- Laryngeal edema is a potentially life-threatening complication of HAE and more than 50% patients will have at least one episode of laryngeal edema in their life time.
- Prodromal symptoms (such as numbness, tingling sensation, pain and formation of faint erythematous serpiginous to annular non pruritic rash resembling erythema marginatum) may be seen in up to 50% of all patients.

Swelling in the lips and eyes in a child with HAE

Swelling over hand in a child with HAE

Swelling over bilateral eyelids in a child with HAE



Erythema marginatum over knee joint in a patient with HAE

WHEN TO SUSPECT HAE?

- History of unexplained recurrent cutaneous or mucosal angioedema attacks with onset of symptoms in childhood/ adolescence
- Family history (Please note that family history may be absent in 20-25% of patients)
- Recurrent and painful abdominal symptoms
- Occurrence of upper airway edema
- Failure of angioedema to respond to antihistamines, glucocorticoids, or epinephrine
- Presence of prodromal signs or symptoms before angioedema episodes
- Absence of urticarial (wheals) and pruritus during angioedema

PLEASE NOTE

- A patient who has difficult to control angioedema (without urticaria) should always be referred to a specialist for evaluation of HAE.
- A patient who has developed angioedemas following use of angiotensin convertase inhibitors, drug induced angioedema should be strongly considered.

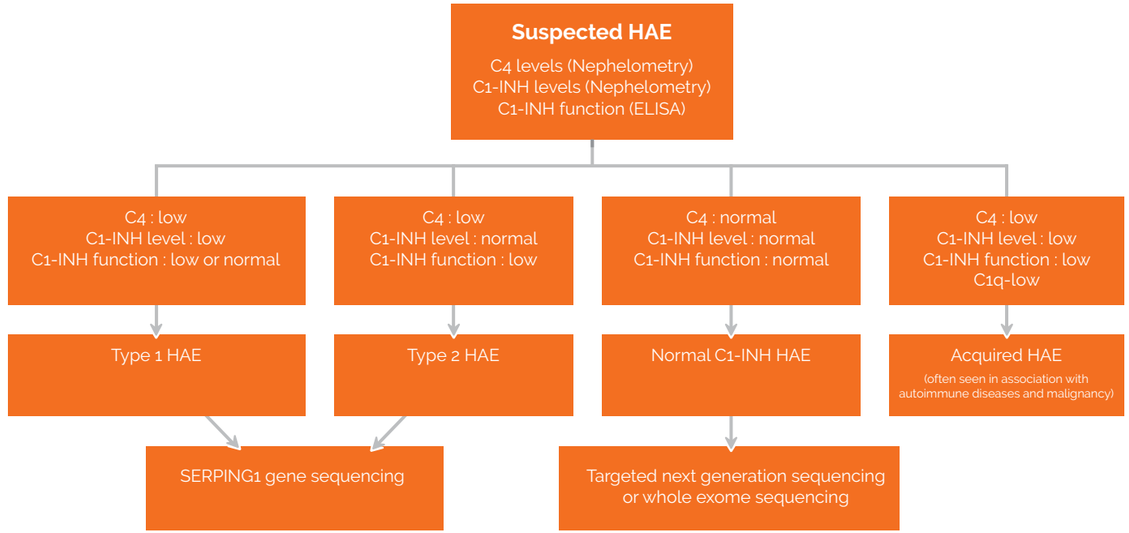
DIAGNOSIS OF HAE

Screening test: C4 levels and C1-inhibitor levels (both by nephelometry); C1-inhibitor function (by Enzyme linked immunosorbent assay, ELISA). If C1-inhibitor function test assay is not readily available, this test may be carried out when C4 is low with normal C1-inhibitor levels with high suspicion for HAE.

It is not recommended to measure C1q levels routinely. C1q may be low in some cases of acquired angioedema and is usually normal in HAE.

POINTS TO REMEMBER

- Measuring C4 alone is 75-80% sensitive
- It is recommended to repeat the tests during an episode of angioedema if initial results are normal and there is high suspicion for HAE.
- C1-INH levels are not reliable during infancy.



- **Availability of tests:** All tests mentioned above including genetic tests are available at the Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh
- C4, C1-INH levels and C1-INH function tests are also available in a few commercial laboratories in the country
- Genetic tests are also being carried out by a few commercial laboratories in the country

MANAGEMENT OF HAE

Acute/on-demand treatment
(for termination of acute episodes)

Short-term prophylaxis
(to be given in situations where an attack is expected to occur such as during the dental procedures or endotracheal intubation)

Long-term prophylaxis
(for prevention of attacks)

PLEASE NOTE

- There is no known permanent cure for HAE
- Goals of treatment are to minimise episodes of angioedema, prevent any disease related mortality and improve quality of life of patient.

ON-DEMAND TREATMENT

- Ideally all acute episodes of angioedema should be treated.
- The only drug available for acute/on demand treatment in India is fresh frozen plasma (FFP).
- FFP contains 1 unit of C1-INH protein in each ml. In some observational studies it has been found to be effective in terminating acute episodes of HAE including laryngeal edema [Dose: 10-20 ml/kg (4-5 units in adults)].
- The dose can be repeated after 12 hours if there is no appreciable improvement.
- Considering the potential adverse effects associated with frequent use of FFP, it is advisable to use FFP during a life-threatening episode of angioedema such as involvement of larynx and tongue and severe abdominal attack.
- When plasma derived C1-inhibitor concentrate would be available in India, this can be used in a dose of 20 units per Kg body weight, maximum dose 1000 units (intravenous).
- **It has been observed that attenuated androgens [danazol (200-400 mg) or stanozolol (2-4 mg)] used at the onset of attack may abort an ongoing episode of angioedema. These drugs are not effective in an established episode of angioedema.**
- **Early use of high dose intravenous or oral tranexamic acid (1000 mg every 3-4 hrs for 12-18 hrs) may also lead to resolution of symptoms in milder episodes.**
- **In these contexts, it is important to identify a prodrome (such as erythema marginatum, severe fatigue or pricking sensation).**

Corticosteroids, antihistamines and epinephrine are not effective for the management of acute episodes of HAE and must not be used.

SHORT-TERM PROPHYLAXIS

- Short term prophylaxis is recommended before a surgical or dental procedures or any invasive medical interventions (such as endoscopy) as these procedures may trigger an acute attack.
- Risk of developing angioedema is very high in the first 24-48 hours after the procedure.
- Plasma derived C1-INH concentrate, when available, is an effective treatment option for short term prophylaxis.
- At present, attenuated androgens [danazol 200-400 mg or stanozolol 2-4 mg or doubling the dose of these drugs if a patient is already taking them as long-term prophylaxis], FFP (10-20 ml/kg) or tranexamic acid [30-50 mg/kg/day (maximum 3-4.5 gm/ day) or doubling the dose if a patient is already taking tranexamic acid as long-term prophylaxis] may be used for short term prophylaxis

- Prophylaxis should be initiated 2 days prior to the anticipated date of procedure and should be continued 5 days later.

LONG-TERM PROPHYLAXIS

- There are no strict guidelines on indications for initiating long-term prophylaxis. However, it may be reasonable to start long-term prophylaxis in patients who experience at least more than one episode of angioedema every month or who has life threatening laryngeal attacks.
- It is better to keep a low threshold for initiating long term prophylaxis till better on demand treatment options are available in India.
- Commonly reported side effects of androgens are weight gain, acne, virilization, menstrual irregularities, hirsutism, hepatic abnormalities, growth retardation, behavioral and mood alterations, headache and cardiovascular risk.
- Monitoring should be done once every 6 months (blood pressure, weight, height, liver function tests, lipid profile, alpha fetoprotein, liver ultrasonography.
- Tranexamic acid is less effective but safer as compared to attenuated androgens.
- Tranexamic acid is a safe and preferred option for long term prophylaxis in children, during pubertal age group, during pregnancy and while breastfeeding.
- There is preliminary experience that a combination of tranexamic acid and attenuated androgens may be more efficacious than either of the 2 drugs used alone.

Drugs available for long-term prophylaxis in India at present:

Danazol:
50 mg 2-3 times a week to 600 mg per day

Stanozolol:
0.5 mg 2-3 times a week to 4 mg per day

Tranexamic acid:
30-50 mg/kg/day (Maximum 3 gm per day)

PLEASE NOTE

- Androgens are contraindicated during pregnancy and breast feeding.
- Avoid triggers: such as trauma, exertion, stress, oral contraceptive pills, angiotensin convertase enzyme (ACE) inhibitors. Triggers are usually patient specific. These must be identified and avoided.