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Lecture Notes in Allergy



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Contents

SECTION 1: INTRODUCTION

1. **The Immune System in Allergy** 3
   Ankur Kumar Jindal, Samipa Samir Mukherjee
2. **Epidemiology of Allergy** 10
   PA Mahesh, Mohammed Kaleem Ullah

SECTION 2: RESPIRATORY ALLERGIES

3. **Allergic Rhinitis** 19
   Sowmya A Nagarajan
4. **Snorers and Mouth Breathers: An Approach** 30
   M Arif Ahmed, Gayatri S Pandit
5. **Chronic Rhinosinusitis in Children** 36
   Saba Fatima Khanam, Gayatri S Pandit
6. **Under-5 Wheeze** 42
   Srinivasa Jakka
7. **Childhood Asthma** 47
   Pillarisetti Naveen Saradhi
8. **Childhood Allergic Bronchopulmonary Aspergillosis** 56
   Pillarisetti Naveen Saradhi, Shruti Kotapalli

SECTION 3: SKIN AND EYE

9. **Atopic Dermatitis** 65
   Peter Arkwright
10. **Contact Dermatitis** 77
    Dipti Pujari
11. **Urticaria** 84
    Ravali Yalamanchili
12. **Ocular Allergies** 92
    Zain Khatib

SECTION 4: SYSTEMIC DISEASES

13. Food Allergy **101**
M Arif Ahmed, Vikram Patra

14. Drug Allergy **112**
M Arif Ahmed

15. Anaphylaxis in Children **124**
Anjul Dayal, Shaheera Eram

16. Insect Venom Hypersensitivity **131**
S Narmada

SECTION 5: ALLERGIC MIMICS

17. Hereditary Angioedema **139**
Ankur Kumar Jindal

18. Nursery School Syndrome **144**
Shalini Tyagi

SECTION 6: INVESTIGATIONS

19. Laboratory Diagnosis of Allergic Diseases **151**
M Arif Ahmed

20. Skin Prick Test **158**
Spurthi Chitta

SECTION 7: THERAPEUTICS

21. Pharmacotherapy **165**
Dipti Pujari

22. Allergen Immunotherapy **176**
PC Kathuria

23. Biological Therapies in Allergic Diseases **185**
Vikram Patra

SECTION 8: EVALUATION

24. Objective Structured Clinical Exam **195**
Ankur Kumar Jindal, Srinivasa Jakka, Sowmya A Nagarajan, S Narmada, Dipti Pujari, Gayatri S Pandit

Index **209**

SECTION 5

Allergic Mimics

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17
CHAPTER

Hereditary Angioedema

Ankur Kumar Jindal

INTRODUCTION

Hereditary angioedema is commonly confused with allergic reaction and wrongly investigated and treated as food allergy. I should be considered in any patient with repeated swellings in absence of a rash.

DEFINITION

Angioedema is defined as subcutaneous and/or submucosal swelling that is typically localized and episodic.

PATHOPHYSIOLOGY

Angioedema is caused by leakage of fluid from capillaries located in deep layers of skin because of an increase in vascular permeability.

CLASSIFICATION

It can be broadly classified as mast cell mediator-mediated (commonly referred to as allergic angioedema) or bradykinin-mediated. Mast cell mediator-mediated angioedema is more common than bradykinin-mediated angioedema.

Bradykinin-mediated angioedema can broadly be categorized into hereditary angioedema (HAE) and acquired angioedema (AAE).

Hereditary angioedema is classified into two types: HAE with C1-inhibitor deficiency (C1-INH-HAE; type I caused by reduced levels of C1-INH protein and type 2, wherein C1INH protein levels are normal but dysfunctional). A mutation in the *SERPING1* gene, encoding the C1 inhibitor (C1-INH) protein, accounts for >95% of all HAE cases. A large proportion (80%) of HAE patients have a suggestive family history as it has an autosomal dominant inheritance and the rest may have a *de novo* defect in the *SERPING1* gene and these patients have no suggestive family history.

These are uncommon potentially life-threatening disorders.

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ONSET

Most cases of HAE (>50%) have onset of symptoms in childhood, however, most often they get diagnosed when they reach adulthood.

PREVALENCE

The prevalence of HAE worldwide is approximately 1:10,000 to 1:50,000. No national prevalence data for India or other developing countries are available. However, based on the global prevalence of HAE, it has been suggested that India has 27,000 to 135,000 HAE patients. Most of these patients remain undiagnosed.

Hereditary angioedema with normal C1-inhibitor levels and activity (nl-C1INH-HAE) is an extremely rare disorder.

CLINICAL PRESENTATION

Patients with HAE usually manifest with recurrent episodes of swelling of the hands, feet, eyes, lips, tongue, and genitalia. These episodes are typically not associated with itching or urticaria; they evolve slowly over 12–24 hours and subside over 3–5 days. Gastrointestinal tract involvement can lead to excruciating pain abdomen often associated with abdominal distension, vomiting, diarrhea, or sometimes constipation. Involvement of the larynx leads to a potentially life-threatening episode of choking and in the past, the mortality because of laryngeal edema used to be as high as 30%. This has considerably reduced with the availability of better first-line treatment options in many countries. However, mortality due to HAE in India continues to be a major concern.

Most angioedema episodes in patients with HAE are spontaneous. A proportion of patients may experience triggers for their acute episodes. These include trauma, stress, hormonal changes, and certain foods. Menstruation is a common trigger for females. Estrogen-containing drugs and angiotensin-converting enzyme (ACE) inhibitors are contraindicated in HAE.

Angioedema episodes in HAE are often associated with prodromal symptoms. These include anorexia, alteration in mood, fatigue, malaise, and arthralgia. Erythema marginatum is a specific prodromal symptom that may be seen in 50–60% of patients in the Western population. In our experience, it has been observed in up to 20% of all patients with HAE.

DIAGNOSIS

Hereditary angioedema relies on a good clinical history and a strong clinical suspicion. The suspicion of HAE should be made in a patient who has a history of recurrent swelling of the skin (hands, feet, face, and genitals), gastrointestinal episodes (abdominal pain), and laryngeal swelling without any itching or urticaria.

Clinical suspicion of HAE would be strengthened by the presence of one or more of the following features:

- Suggestive family history
- Early age of onset of clinical features

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TABLE 1: Differentiating factors for types of hereditary angioedema (HAE).

	C1-INH levels	C4	C1-INH function
Type 1	Low	Low	Low
Type 2	Normal or high	Low	Low
Normal C1-INH-HAE	Normal	Normal	Normal

- Unresponsiveness to antihistamines, adrenaline, and glucocorticoids
- Presence of trigger and prodrome

The international guidelines for the diagnosis and management of HAE propose testing for levels of C4 and C1-INH along with C1-INH function in every patient with suspicion of HAE **(Table 1)**.

Explanation: However, availability and access to all three tests for screening HAE patients in India is a challenge. Hence, the recently published consensus statement from India suggests using C4 levels to screen patients with HAE.

Assessment of C4 alone as a screening test for HAE has approximately 80% sensitivity with normal C4 levels in up to 20% of patients with type 1 and 2 HAE. The sensitivity of the C4 test, however, can be increased if the test is done during an acute episode.

LABORATORY

C4 and C1-INH levels are usually assessed by nephelometry while functional assay for C1-INH is carried out by enzyme-linked immunosorbent assay (ELISA).

A genetic test is not mandatory to diagnose a patient with HAE. However, genetic testing is required for antenatal diagnosis, for diagnosing HAE in young infants (where complement studies may not be reliable), and for diagnosing normal C1-INH HAE (previously known as type 3 HAE). Next-generation sequencing is the preferred technique used for establishing the genetic diagnosis.

MANAGEMENT OF HEREDITARY ANGIOEDEMA

The primary goal of managing HAE is to prevent mortality related to the disease and improve the quality of life. The availability of better first-line therapeutics in developed countries has significantly reduced mortality associated with HAE. However, when first-line medications are not readily available, mortality remains a concern. Plasma-derived C1-INH (pd C1-INH) concentrate is now available in India and is increasingly used for the management of acute episodes.

Management of HAE is based on three key principles **(Table 2)**:

1. *Treatment of acute attacks (i.e., on-demand therapy)*: On-demand therapy focuses on addressing acute attacks to alleviate symptoms and minimize their impact. Ideally, all angioedema attacks need on-demand therapy. The drugs that are used for on-demand therapy are:
   a. C1-INH concentrate: Preferred choice for managing acute attacks in HAE in many developed countries

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TABLE 2: Drugs used in the management of hereditary angioedema (HAE).	
Acute treatment of attacks (on demand)	• Plasma-derived C1-INH • Fresh frozen plasma • Ecallantide (plasma kallikrein blocker) • Icatibant (competitive antagonist of B2 receptor)
Short-term prophylaxis (preprocedural)	• Plasma-derived C1-INH • Fresh frozen plasma • Attenuated androgens
Long-term prophylaxis (suppression of attacks)	• Lanadelumab (monoclonal antibody against plasma kallikrein) • Berotralstat (inhibits plasma kallikrein) • Tranexamic acid • Attenuated androgens

   b. Ecallantide (plasma kallikrein blocker) and icatibant (competitive antagonist of B2 receptor) are indicated for on-demand treatment. However, these are not available in India currently.
   c. Fresh frozen plasma (FFP) (10–20 mL/kg, containing 1 unit of C1-INH per mL) can be used for the management of acute attacks of HAE. Due to potential side effects including infusion reactions, anaphylaxis, risks of transmission of infections, and volume overload, it is recommended to be used in acute life-threatening situations such as laryngeal edema.
2. *Short-term prophylaxis (STP)*: STP is needed in situations where there is a predictable risk of developing life-threatening laryngeal edema. High-risk situations involving laryngeal manipulation, such as those requiring general anesthesia and laryngeal intubation, warrant STP. pd C1-INH concentrate is the best possible option for STP in India and should be administered soon before the intervention (dose 10–20 units/kg). The dose may be repeated if required.

   Fresh frozen plasma and attenuated androgens in combination may also be used for STP. For patients who are taking attenuated androgens as LTP, doubling the dose 2 days before the anticipated procedure and continuing for 5 days post procedure is recommended. In cases where patients are not using attenuated androgens, it should be initiated 2 days before the procedure (dose: Stanozolol 2 mg/day) and continued for 5 days post procedure. FFP administration (@ 10 mL/kg twice daily) is recommended 1–2 days before the procedure and a single dose on the day of the procedure. FFP administration post procedure may be considered on a case-to-case basis, especially for patients undergoing laryngeal manipulation.
3. *LTP*: It includes the administration of drugs continuously to prevent the development of attacks or to reduce their severity, especially for patients with frequent and debilitating episodes.
   a. Tranexamic acid: Tranexamic acid, an antifibrinolytic agent, inhibits plasmin production, reducing bradykinin production. While less effective than attenuated androgens, the better safety profile of tranexamic acid makes it a preferred choice especially in children, adolescents, and

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pregnant women (if required). A 30–50 mg/kg/day dose in 2–3 divided doses (maximum dose 3 g/day) is recommended.

b. Attenuated androgens: These drugs may increase C1-INH production and are commonly used for LTP. Stanozolol (dose 0.5 mg every other day to 4 mg/day) and danazol (100 mg every other day to 600 mg/day) are two common attenuated androgens used for LTP. Dose-limiting side effects include various complications and a close watch on growth and blood pressure. Monitoring of liver enzymes, and liver ultrasound also become necessary during chronic use of the drug.

c. Newer agents: Lanadelumab (300 mg subcutaneously 2–4 weekly) is a fully humanized monoclonal antibody targeting plasma kallikrein and has been approved for LTP in adolescents and adults.

   Berotralstat (BCX7353) is another promising LTP. It is a highly selective inhibitor of plasma kallikrein. In phase 3 randomized controlled trial, orally administered berotralstat 150 mg once daily decreased the frequency of HAE attacks significantly and exhibited a favorable safety profile.

   An *in vivo* gene editing therapeutic called NTLA-2002 is based on CRISPR (clustered regularly interspaced short palindromic repeats) and CRISPR-associated protein 9. With just one dosage, NTLA-2002 aims to permanently suppress angioedema episodes by targeting the kallikrein B1 (*KLKB1*) gene. No serious side effects were reported and total plasma kallikrein was effectively suppressed.

d. *Other general measures*: Identification of potential triggers and counseling to avoid them is essential for the management of patients with HAE. ACE inhibitors and estrogen-containing pills must be avoided in all patients.

KEY POINTS

- ❑ HAE is grossly under-recognized in India.
- ❑ Most patients with HAE have symptom onset in childhood.
- ❑ HAE should be suspected in a patient with a history of recurrent skin swelling (hands, feet, face, and genitals), gastrointestinal episodes (abdominal pain), and laryngeal swelling without any itching or urticaria.
- ❑ C4 is a simple screening test for HAE.
- ❑ pd C1-INH concentrate is now available in India and is a useful drug for on-demand treatment and STP.

FURTHER READINGS

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Lecture Notes in
Allergy

As a stakeholder of allergies in the community, I could sense the void in the knowledge of allergic diseases at every level. Hence, a need was created to write lecture notes. The characteristic feature is the points followed by the explanation. During their studies, students need to go through every line and understand the subject. However, during examination or revision within a limited time, all they need to do is read the points and key summary. The book comes with an audio lecture by each of the authors to provide clarity on the subject. The practitioners lack time for the detailed reading of a reference book on a subject never taught during college. This book provides the information needed to manage the patient at hand. A set of OSCE-type questions is provided to stimulate your mind. All in all, the information is just enough for not only to get through examinations but also to manage the patients.



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