Hereditary Angioedema in a Pediatric Patient: A Case Study on Diagnosis, Treatment, and Genetic Considerations

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Introduction

Angioedema, a condition characterized by swelling of deeper layers of the skin, often involves the face, lips, eyes, and throat. While it can be caused by an allergic reaction or other triggers, the condition presents unique diagnostic and management challenges, especially when it occurs in children. In this article, we explore a case study of a three-year-old child with recurrent episodes of eye swelling, investigate the different types of angioedema, and delve into the complexities of diagnosing and treating hereditary angioedema (HAE), particularly in a resource-limited setting like India.

Case Presentation: A Three-Year-Old with Sudden Bilateral Eye Swelling

A three-year-old child presented to the emergency room with sudden bilateral eye swelling that developed over a few hours. This swelling was preceded by itching in the eyes, which worsened after the child rubbed her eyes, followed by redness. This was the second such episode in two months. The child had previously been diagnosed with allergic rhinitis and moderate asthma, which were managed with nasal drops and inhalers. However, this episode occurred without any respiratory exacerbation or rhinitis, distinguishing it from prior incidents.

The mother expressed concern after a doctor suggested that the child might develop life-threatening symptoms, including throat constriction, similar to anaphylaxis. This prompted further investigation. Upon evaluation, clinical findings suggested angioedema—a condition characterized by swelling of deeper layers of skin, but without the presence of rashes, which is uncommon for mast cell-mediated angioedema.

Differentiating Types of Angioedema

The primary challenge in this case was determining the type of angioedema the child was experiencing. Angioedema can be categorized as either mast cell-mediated or bradykinin-mediated. Mast cell-mediated angioedema is often allergic, triggered by IgE-mediated reactions to environmental factors or foods. This type presents rapidly, typically within hours, and is often associated with hives or urticaria. However, the absence of rashes in this case suggests that mast cell-mediated angioedema may not be the cause.

Bradykinin-mediated angioedema, in contrast, presents more slowly, without hives, and can last for 24 to 48 hours. This form of angioedema is often hereditary but can also be acquired, especially in older individuals. Given the child’s history of atopic conditions like allergic

rhinitis and asthma, a mast cell-mediated cause seemed more likely, though further investigation was required.

Types of Angioedema

The different types of angioedema:

1. **Mast Cell Mediated Angioedema**:
    - **IgE-mediated**: Triggered by allergens and often seen in conditions like **allergic rhinitis**. Onset is typically rapid, within hours, and resolves quickly with **antihistamines** and **steroids**.
    - Associated with **urticaria** and **rashes**.
2. **Bradykinin-Mediated Angioedema**:
    - Includes **Hereditary Angioedema (HAE)**, which is often **genetic** and **autosomal dominant**. It is slower to progress and can persist for up to **48 hours**. This type does not present with **rashes** but may involve **severe abdominal pain** and **vomiting**.
    - **Acquired Angioedema**: Often seen in older individuals, may be associated with **malignancies** or **autoimmune conditions**.
    - **Functional C1 Inhibitor Deficiency**: Can present in **Hereditary Angioedema Type 2**, where the C1 inhibitor is normal, but its function is impaired.
3. **Drug-Induced Angioedema**:
    - Commonly caused by **ACE inhibitors** or **NSAIDs**. This type often leads to **laryngeal edema**, which can be life-threatening if not managed promptly.
4. **Idiopathic Angioedema**:
    - Cases where no underlying cause can be identified, and **C1 inhibitor levels** are normal.

Hereditary Angioedema: Genetic Considerations

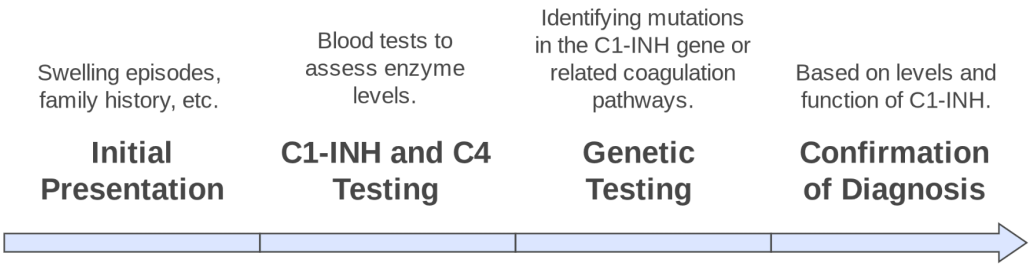
The panel highlighted the importance of understanding the genetic basis of hereditary angioedema:

- Type 1 HAE: Characterized by low C1 inhibitor and low C4 levels.
- Type 2 HAE: Characterized by normal C1 inhibitor levels but functional deficiency.
- Type 3 HAE: A rare form where C1 inhibitor levels and C4 levels are normal, and the condition is associated with coagulation pathway abnormalities.

Clinical Challenges and Late Diagnosis of Hereditary Angioedema

Diagnosing hereditary angioedema in children is challenging, particularly when symptoms like swelling, abdominal pain, or vomiting occur intermittently and are not accompanied by hives. The slow progression of symptoms may delay diagnosis, as physicians often treat the symptoms as allergic reactions or gastrointestinal issues.

The case of an eight-year-old child who had recurrent vomiting and abdominal pain, initially thought to be due to gastrointestinal problems, serves as a reminder of the difficulty in diagnosing hereditary angioedema. When a low C4 level was discovered, the diagnosis of bradykinin-mediated angioedema was confirmed, demonstrating the importance of considering HAE in patients with unexplained, recurrent symptoms.



Family History and Genetic Factors

Family history plays a crucial role in diagnosing hereditary angioedema. In this case, the child's maternal family history pointed to a genetic predisposition, as the child's maternal uncle also had similar symptoms. Hereditary angioedema can skip generations, and affected individuals may not show symptoms until later in life. A thorough family history is essential for identifying potential genetic links, which can guide diagnosis and treatment.

Family history is particularly important in cases of hereditary angioedema, as it helps clinicians recognize genetic patterns that may not be immediately evident in a child's clinical presentation. Genetic testing can confirm the diagnosis and inform treatment decisions.

Management of Hereditary Angioedema (HAE)

1. **Acute Management**:

- The **first-line treatment** for **IgE-mediated angioedema** is **epinephrine**, followed by **antihistamines** and **steroids**.

- For **bradykinin-mediated** angioedema, **C1 inhibitor concentrate** is the most effective treatment.

- **Fresh Frozen Plasma (FFP)** can be used in resource-limited settings if **C1 inhibitor concentrate** is unavailable.

2. **Prophylactic Management**:

    - **C1 inhibitor concentrate** can also be used as **prophylaxis** to prevent acute attacks, especially for patients with frequent episodes.

    - **Tranexamic acid** and **dianozol** (an androgen) are used for **short-term prophylaxis**, but they have limited efficacy in **children** due to potential **side effects**.

    - **Bradykinin receptor antagonists** and **calicrine inhibitors** are not yet available in India, but they are being explored in **clinical trials**.

Conclusion

Hereditary angioedema is a rare but important condition that should be considered in children with recurrent episodes of swelling, especially when other allergic causes are not supported by clinical findings. A thorough family history and diagnostic tests such as C1-INH and C4 levels are crucial for accurate diagnosis. Early administration of C1-INH therapy in this case alleviated the child's symptoms and prevented further complications, emphasizing the importance of early intervention. Increased awareness among clinicians and improved access to genetic testing and treatment options are essential for better managing hereditary angioedema in India.

Q&A Highlights:

Q1: How do we differentiate between mast cell-mediated and bradykinin-mediated angioedema?

- **A1:** The key difference lies in the onset, duration, and associated symptoms:

    - **Mast Cell-Mediated (Histamine-Induced)** angioedema tends to have a rapid onset within **hours** and resolves quickly. It is often accompanied by **urticaria (hives)** or **rash** and is typically triggered by allergens.

- **Bradykinin-Mediated Angioedema** (often hereditary) progresses slowly over **24-48 hours** and does not usually present with **rash** or **urticaria**. It often involves severe **abdominal pain** and **vomiting** and can have **laryngeal edema**, which is a medical emergency. The response to **epinephrine** is minimal in bradykinin-mediated angioedema, whereas histamine-induced angioedema usually improves rapidly with **epinephrine**.

Q2: What are the common triggers for angioedema in pediatric patients?

- **A2:** Common triggers include:
  - **Insects**: Stings or bites from bees, wasps, or ants can trigger localized or systemic angioedema, especially in individuals with a **mast cell disorder**.
  - **Food allergies**: Foods like **milk**, **nuts**, and **shellfish** can provoke an allergic response, potentially leading to angioedema.
  - **Medications**: **ACE inhibitors**, **NSAIDs**, and **radiocontrast dyes** can induce drug-induced angioedema.
  - **Environmental allergens**: Exposure to dust mites, pollen, and animal dander can trigger **mast cell-mediated** reactions, causing angioedema in susceptible children.

Q3: How do we manage hereditary angioedema (HAE) in a pediatric patient?

- **A3:** The management of **hereditary angioedema (HAE)** involves:
  - **Acute management**: The first-line treatment for **bradykinin-mediated** angioedema is **C1 inhibitor concentrate** or, if unavailable, **fresh frozen plasma (FFP)**. **Epinephrine** can be used for **histamine-mediated** angioedema.
  - **Prophylactic management**: For children with recurrent episodes, **C1 inhibitor concentrate** can be used as a prophylactic treatment. **Tranexamic acid** and **dianozol** (an androgen) can also be used for **short-term prophylaxis**, although these are less effective in children due to potential side effects.

Q4: What is the role of genetic testing in diagnosing hereditary angioedema (HAE)?

- **A4: Genetic testing** is crucial for confirming **hereditary angioedema (HAE)**. Testing for **C1 inhibitor (C1-INH)** levels and **C4 levels** is typically the first step:
    - **Low C1-INH levels** and **low C4 levels** are characteristic of **Type 1 HAE**.
    - **Normal C1-INH levels** but **functional deficiency** may suggest **Type 2 HAE**.
    - In rare cases, **Type 3 HAE** may be suspected, where **C1-INH levels** and **C4 levels** are normal, and further **whole genome sequencing** may be required to identify mutations in genes related to the **calicrine pathway**, such as **factor 12** or **angiopoietin** genes.

Q5: What is the treatment for angioedema when C1 inhibitor concentrate is not available in India?

- **A5:** In settings where **C1 inhibitor concentrate** is not available, **fresh frozen plasma (FFP)** can be used as a substitute, although it is less effective. For acute management, **epinephrine**, **antihistamines**, and **steroids** can be used to control symptoms of **histamine-induced angioedema**. In resource-limited settings, **tranexamic acid** and **dianozol** are used for **prophylaxis**. **Genetic testing** for **C1-INH deficiency** is essential, but due to the high cost, it may not always be accessible for all patients.

Q6: How can we approach the management of idiopathic angioedema?

- **A6: Idiopathic angioedema** is a diagnosis of exclusion. If **C1 inhibitor levels** and **C4 levels** are **normal**, and there is no identifiable cause (such as **allergy** or **infection**), the condition is considered idiopathic. Management involves:
    - **Epinephrine** for acute symptoms.
    - **Steroids** and **antihistamines** to manage swelling and inflammation.
    - **Prophylactic treatments** like **tranexamic acid** and **dianozol** may be considered, although these have limited efficacy in **children**.

Q7: What are the common challenges in diagnosing and treating hereditary angioedema in India?

- **A7:** The main challenges include:

- **High cost** of **C1 inhibitor concentrate** and **genetic testing**, which can make treatment unaffordable for many patients.

- **Lack of awareness** among healthcare providers, leading to delayed diagnoses. Many children are initially misdiagnosed with common allergies or respiratory conditions.

- Limited availability of **specialized tests**, like **C1-INH functional assays** and **genetic tests**, which are necessary for accurate diagnosis.

- **Resource constraints** in rural or low-income settings, where **fresh frozen plasma (FFP)** may be the only alternative to **C1 inhibitor concentrate**, though it is less effective.

Q8: How can we improve awareness and diagnosis of hereditary angioedema (HAE) in the Indian healthcare system?

- **A8:** Improving awareness involves:

    - **Education and training** for pediatricians, allergists, and other healthcare providers about **angioedema**, its types, and triggers.

    - **Routine screening** for **C1-INH deficiency** in patients with recurrent swelling or unexplained **abdominal pain**.

    - Increased availability and **affordability of diagnostic tests**, including **C1 inhibitor** assays and **genetic testing**.

    - Collaboration with **geneticists** and **immunologists** to facilitate early diagnosis and **genetic counseling** for affected families.

Q9: Are there any specific triggers that pediatricians should be aware of in children with hereditary angioedema?

- **A9:** Yes, common triggers include:

    - **Physical trauma** or **stress**.

    - **Insect stings** (especially **bees** and **wasps**).

    - **Infections**, including respiratory infections, which can exacerbate symptoms.

- **Hormonal changes**, especially in **adolescent girls**.
- **Certain medications**, including **NSAIDs** and **ACE inhibitors**.

Q10: Can hereditary angioedema lead to complications in the absence of proper treatment?

- **A10:** Yes, if left untreated or inadequately managed, **hereditary angioedema** can lead to severe complications, including:
  - **Airway obstruction** due to **laryngeal edema**, which can cause **asphyxiation**.
  - **Chronic abdominal pain** and **vomiting**, which can lead to unnecessary surgical interventions.
  - **Failure to thrive** or **growth delays** in children due to recurrent episodes and lack of proper management.
  - **Life-threatening episodes** if attacks occur in critical areas such as the **throat** or **lungs**.