Idiopathic anaphylaxis
EVALUATION

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EVALUATION:

- All patients suspected of having Idiopathic anaphylaxis should be referred to an allergy specialist, because :
- all possible triggers of anaphylaxis and
- disorders that mimic anaphylaxis should be considered and ruled out before making the diagnosis.

Patients with possible IA should be supplied with at least two epinephrine autoinjectors and instructed on how and when to use them if symptoms recur, even before they are evaluated by an allergy specialist.

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EVALUATION:

- IA is established only after

performing a comprehensive history, physical examination, review of medical records, and appropriate laboratory tests.

Depending on the allergen that is under consideration, testing may involve skin testing, measurement of allergen-specific serum IgE, component-resolved diagnostics, or challenge procedures.

Evaluate for possible triggers

Evaluate for possible triggers :

- On occasion, patients who were thought to have IA are found to have unusual triggers of anaphylaxis that were initially overlooked.

- We review all ingestions (foods, medications, beverages), activities, and changes to baseline health in the hours before each episode that the patient can recall.

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Symptoms in association with eating:

Symptoms in association with eating:

- **Food-associated triggers should be considered in patients whose reactions occur in close association with eating. Considerations include:**

- **Undeclared or mislabeled food allergens, or "hidden" food allergens, such as peanut in egg rolls, tree nuts in salad dressing, or soy in canned tuna . Patients with food allergy occasionally react to non-food items as well.**

- **nonfood items may contain food ingredients, such as medications, vaccines, cosmetics, craft supplies, and sports equipment. Labeling laws do not apply to these products.**

- **vaccines can contain food allergens, including egg, chicken, cow's milk, and gelatin proteins.**

- **Over-the-counter and prescription medications in tablet and capsule form, some inhaled medications for asthma, and some brands of injectable glucocorticoids can also contain food allergens.**

- **Lactose is a milk sugar derived from milk that is used in many dry-powder inhalers (DPIs), some brands of oral and injectable glucocorticoids, and a few oral medications that are commonly used in atopic patients.**

- **Pharmaceutical-grade lactose is considered to contain very little to no milk protein, on the order of a few parts per million. However, possible reactions in children with severe milk allergy have been reported, and small amounts of milk proteins have been detected in various DPI devices , lactulose solution, and injectable methylprednisolone (Solu-Medrol 40 mg/mL).**

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- **We prefer lactose-free preparations or metered-dose inhalers (MDIs) for patients with asthma and milk allergy.**

- **We also avoid, when practical, other lactose-containing medications (eg, the soluble tablet formulation of lansoprazole, chewable cetirizine, and the 10 mg formulation of montelukast) in highly milk-allergic patients for the same reason.**

- **Propofol** is formulated in a fat emulsion containing soybean oil and egg lecithin and may contain small amounts of soy or egg protein. The package insert still indicates that it is contraindicated in patients with soy or egg allergy.
- Various cosmetics may contain a variety of food-derived ingredients .

- Milk, nut oils, wheat, and soy may be used in cosmetics.

- Children's craft items such as modeling dough may contain wheat. Sometimes egg white is used to smooth finger paints, and chalk may contain casein .

Symptoms in association with eating:

- **Spices, especially members of the Apiaceae (Umbelliferae) family, which include caraway, coriander, and fennel . Other spices that have been implicated in systemic reactions include garlic, onion, mustard, saffron, parsley, and cumin.**

- **Allergens that can cause reactions in some patients with other food allergies, such as pectin or pink peppercorns in some patients with cashew or pistachio allergies, or lupine flour in some patients with peanut allergies (more common in European populations).**

Symptoms in association with eating:

- Food causing anaphylaxis in the setting of **exercise** or when taken in temporal proximity to nonsteroidal anti-inflammatory drugs (**NSAIDs) or alcohol**, but **not with ingestion of the food alone**. The best-described example of anaphylaxis that only occurs when other co-factors are present is wheat-dependent exercise-induced anaphylaxis, which is usually caused by sensitization to the allergen omega-5 gliadin .
- Some experts have suggested that sensitization to omega-5 gliadin be assessed in all cases of apparent IA.

Symptoms in association with eating:

- **Mammalian meat, which can cause delayed (eg, up to several hours after ingestion) anaphylaxis in patients sensitized to the carbohydrate allergen, alpha-gal.**

- **Foods contaminated with aeroallergens (eg, "bee pollen"), which often contains ragweed pollen , flour contaminated with mite allergens (variably called "pancake" syndrome or oral mite anaphylaxis) , or grain products contaminated with insects .**

Symptoms in association with eating:

- **Food additives, such as carmine powder and psyllium .**

- **Allergic reactions to *Anasakis simplex*, a fish nematode, can mimic fish allergy, but symptoms are delayed 2 to 24 hours after the ingestion of fish and testing for specific IgE to fish is negative. This is almost exclusively reported in Spain.**

Medications:

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Medications:

- **Medication triggers that should be considered before labeling a patient with IA include:**

- **Ingestion of over-the-counter medications containing NSAIDs that the consumer did not recognize .**

- **Ingestion of angiotensin-converting enzyme (ACE) inhibitors that can cause angioedema .**

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Other potential triggers :

- Other potential triggers include:
- Exercise (alone and/or in combination with prior ingestion of food or medication)
- Latex exposure
- Undetected insect bites and stings from Hymenoptera, pigeon ticks, or Triatoma.

Rule out disorders that mimic anaphylaxis

Differential diagnosis of anaphylaxis:

1. Common disorders:

Acute generalized urticaria and/or angioedema

Acute asthma exacerbation

Vasovagal syncope (faint)

Panic attack/acute anxiety attack

Differential diagnosis of anaphylaxis:

2.Other respiratory events:

Pulmonary embolism

Pneumothorax

Foreign body aspiration (especially in children)

Vocal cord dysfunction

Epiglottitis

Hyperventilation

Differential diagnosis of anaphylaxis:

3. Cardiac events:

Myocardial infarction

Dysrhythmia

Acute symptoms related to structural disorders (eg, aortic stenosis, hypertrophic cardiomyopathy)

4. Shock

Differential diagnosis of anaphylaxis:

5. Flushing

Perimenopause/Carcinoid syndrome/Autonomic epilepsy/Medications/Alcohol/Medullary carcinoma of the thyroid/Vancomycin flushing syndrome

6. Postprandial syndromes

Scombroidosis /Anisakiasis/Pollen-food allergy syndrome/ Food poisoning/Caustic ingestion (especially in children)

Differential diagnosis of anaphylaxis:

7. Neurologic events:

Seizure

Cerebrovascular event (stroke)

8. Nonorganic disease:

Munchausen syndrome

Psychosomatic episode

Somatoform symptom disorder :

- Some patients describe subjective symptoms that are consistent with IA, but have not had objective signs or symptoms documented, do not have organic disease that can be verified, and do not respond to treatment for IA. For example, patients may report a sensation of throat tightness (ie, globus sensation) and be concerned that their throat may close or they can't breathe. It is essential that these patients be evaluated by an otolaryngologist or other provider in the urgent care setting while the symptom is present if episodes become recurrent. Such patients can be very challenging to manage, utilize the emergency department repeatedly, and may meet criteria for somatoform symptom disorder or panic disorder.

Exclusion of a monoclonal mast cell population

Exclusion of a monoclonal mast cell population:

- For patients with **difficult to control disease, or symptoms that change over time or are especially severe**, we test for monoclonal mast cell disorders .

- To exclude a clonal mast cell disorder, serum tryptase should be measured at baseline and after an episode of symptoms, if not already performed.

Mast cell activation disorders:

- Idiopathic mast cell activation syndrome (IMCAS) is similar to IA, but signs and symptoms do not meet criteria for anaphylaxis, usually because patients do not become frankly hypotensive. To make the diagnosis of IMCAS, there must be transient elevations in mast cell mediators, which return to normal in between episodes. The definition of IMCAS and IA are evolving, and some experts suggest that IA is better classified as a subset of IMCAS .
- Another subset of patients has a monoclonal population of mast cells and can be classified as monoclonal mast cell activation syndrome (MMAS) . Bone marrow biopsy is sometimes required to conclusively exclude a mast cell disorder

Systemic mastocytosis:

- In contrast to IA and mast cell activation disorders, patients with systemic mastocytosis have elevations of serum total tryptase levels that are persistent and are detectable even after resolution of an acute episode .
- Systemic mastocytosis is characterized by a pathologic increase in mast cell numbers in the tissues.

DIAGNOSIS:

- IA is a diagnosis of exclusion, by definition. **Patients must meet clinical criteria for the diagnosis of anaphylaxis and have no identifiable cause.**

- These are the minimum requirements for diagnosis.

- Patients with IA may also have episodes of anaphylaxis caused by known triggers, such as food, medications, and exercise, but **these do not account for all of the anaphylaxis episodes.**

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Available tests for the evaluation of anaphylaxis:

- An anaphylaxis episode can be confirmed, in some cases, by acute measurement of serum tryptase or other mast cell mediators in the hours after an episode of symptoms
- **tryptase**
- Histamine
- N-methylhistamine
- N-methylimidazole acetic acid
- 11-beta-prostaglandin $F_{2\text{-alpha}}$
- Leukotriene E_4
- Platelet-activating factor

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- **The minimal elevation in serum total tryptase level that is considered to be indicative of clinically significant mast cell activation is ≥(2 + 1.2 x baseline tryptase levels).**

- **However, a normal serum tryptase does not exclude the diagnosis of anaphylaxis.**

- **A total tryptase level that is persistently elevated at baseline, rather than only following symptoms, strongly suggests either hereditary alpha tryptasemia or systemic mastocytosis, and further evaluation should be pursued.**

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- **There are also disorders that can cause persistently elevated tryptase levels in the absence of allergic or anaphylactic symptoms, such as chronic kidney disease and certain myelodysplastic syndromes.**

- **Further testing should focus on ruling out specific triggers of anaphylaxis or conditions with similar symptoms. Testing should be limited to the evaluation of specific triggers or disorders that are suspected based on the patient's history and examination, and measurement of a baseline serum total tryptase level**

Classification :

- IA is classified into subgroups based on frequency of episodes and clinical manifestations:

- **Frequent versus infrequent** — Frequent IA has been defined as at least two episodes in the preceding two months or at least six episodes in the preceding year . Patients with IA who do not meet one of these criteria are categorized as having infrequent IA.

Classification :

- **Generalized versus angioedema** — IA-generalized is characterized by prominent urticaria with or without angioedema plus other severe systemic symptoms (cardiovascular, respiratory symptoms, and/or gastrointestinal).
- IA-angioedema is the term given to occasional patients whose episodes are characterized by marked upper airway obstruction due to severe angioedema of the tongue, pharynx, and/or larynx. In the author's experience, this type of IA may involve upper airway angioedema plus gastrointestinal pain and hypotension (possibly due to bowel angioedema and third-spacing of fluid).

- **If the patient's angioedema cannot be readily visualized, particularly if the throat is involved, it is important that it be objectively confirmed at some point, as several other disorders can cause a subjective sensation of throat tightness or swelling. Common etiologies of subjective throat tightness include vocal cord dysfunction and laryngopharyngeal reflux. An endoscopic exam (by an otolaryngologist or other appropriately trained clinician) during an episode of symptoms is critical to distinguishing these disorders from actual angioedema and should be pursued whenever feasible.**

- **In patients whose symptoms are predominantly angioedema without urticaria, disorders causing bradykinin-induced angioedema, such as hereditary angioedema (due to C1 inhibitor deficiency or other defects) and ACE inhibitor-induced angioedema, should be considered in the differential diagnosis.**
- **A serum level of C4 is a reasonable screen for C1 inhibitor deficiency (inherited or acquired), although there are several forms of episodic angioedema in which complement studies are normal.**


Thank You!