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Anaphylaxis vulnerability-possible treatment and prevention

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Abstract
Adverse reactions to drugs require that their mechanisms be elucidated, particularly when anaphylaxis is suspected. Early diagnosis can be achieved by plasma histamine measurements. Unfortunately, the short plasma half-life of histamine and the difficulties in handling the sample usually preclude this measurement, although a sensitive radioimmunologic kit is routinely available. It has been recently suggested that mast cell tryptase, a component of the mast cell granules, could provide an alternative to histamine determination. Angioedema of the face is such that the boy cannot open his eyes. This reaction was caused by an allergen exposure. Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Diagnosis is based on the presenting symptoms and signs after exposure to a potential allergen. The symptoms are caused by the sudden release of chemical substances, including histamine, from cells in the blood and tissues where they are stored. The release is triggered by the interaction between an allergic antibody called Immunoglobulin E (IgE) and the substance (allergen) causing the anaphylactic reaction. Anaphylaxis is a serious systemic allergic reaction that is rapid in onset and may cause death. The diagnosis of anaphylaxis during the acute event is based on the clinical presentation and a history of a recent exposure to an offending agent. There are no laboratory tests available in an emergency department or clinic setting to confirm a diagnosis of anaphylaxis in real time. Laboratory tests in serum, plasma, and possibly urine obtained during or shortly after the acute event can however help to support the clinical diagnosis of anaphylaxis. These tests can also help identify anaphylaxis in the presence of other disorders that have overlapping clinical presentations, such as severe asthma or myocardial infarction. In addition, these tests may provide evidence for anaphylaxis as a cause of death. This topic reviews the laboratory tests that can be used to support the clinical diagnosis of anaphylaxis in both adults and children. These tests are different from those that identify sensitization to histamine measurements the inciting allergen, namely measurements of allergen-specific immunoglobulin E (IgE), which are reviewed.

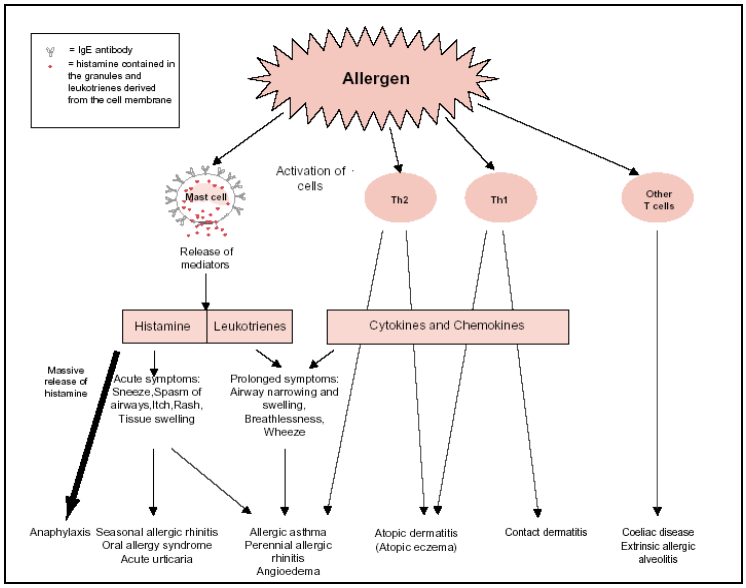
Keywords: drugs, histamine measurements, angioedema, IgE, allergen, asthma, exposure, radioimmunologic kit

Introduction

The principal effector cells of systemic anaphylaxis certainly include mast cells and likely basophils. The various preformed and newly generated mediators secreted by these cells cause many of the signs and symptoms of systemic anaphylaxis. The pathophysiology of anaphylaxis is reviewed in detail separately. Mediators released during anaphylaxis — Mast cells and basophils degranulate upon activation, releasing tryptase along with histamine from intracellular granules into the extracellular environment. Two of the most abundant and best characterized preformed granule mediators released by these cells during anaphylaxis are tryptase and histamine. Elevations in tryptase and histamine can sometimes be detected in blood samples obtained shortly after the onset of symptoms. Also, elevated levels of histamine, histamine metabolites (N-methylhistamine and N-methylimidazole acetic acid), the prostaglandin D_2 (PGD_2) metabolite, 11-beta-prostaglandin $F_{2\text{-alpha}}$ (11-beta-$PGF_{2\text{-alpha}}$), and the leukotrienes C_4 (LTC_4) metabolite, leukotrienes E_4 (LTE_4) can be measured in urine or in some cases, in serum or plasma after an anaphylactic event. The symptoms are caused by the sudden release of chemical substances, including histamine, from cells in the blood and tissues where they are stored. The release is triggered by the interaction between an allergic antibody called Immunoglobulin E (IgE) and the substance (allergen) causing the anaphylactic reaction. These chemicals also cause other problems such as a fall in blood pressure, also known as hypotension. The histamine released by your body during an anaphylactic reaction causes blood vessels to widen which leads to a sudden and severe drop in blood pressure. Common anaphylaxis triggers include: Foods – including nuts, milk, fish, shellfish, eggs and some fruits, Medicines – including some antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, Insect stings – particularly wasp and bee stings, General anesthetic, Allergy occurs when a person's immune system reacts to substances (allergens) in the environment which are usually harmless (e.g. food proteins, pollen, dust mites). Anaphylaxis is the most severe form of allergic reaction and is potentially life-threatening. Dec 10, 2009.

Symptoms

Skin rashes and itching and hives, Swelling of the lips, tongue or throat, Shortness of breath, trouble breathing, wheezing (whistling sound during breathing),Dizziness and/or fainting, Stomach pain, vomiting or diarrhea, Feeling like something awful is about to happen.



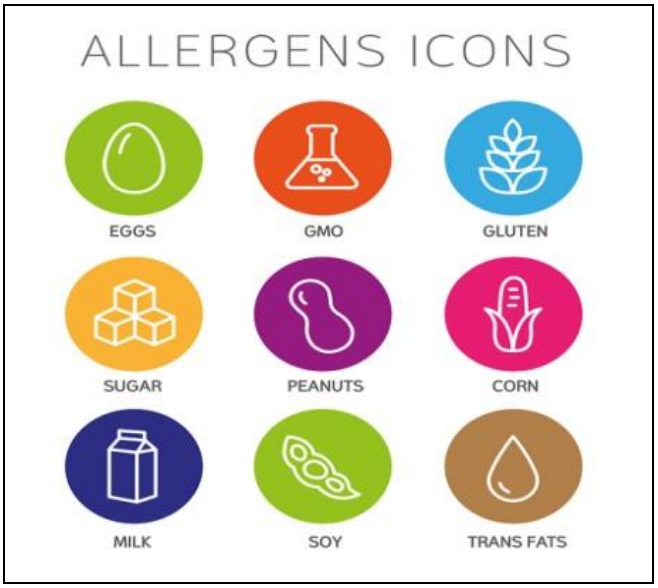


Fig 1

Discussion

Epinephrine is the drug of choice for life-threatening reactions. During an anaphylactic attack, one might receive cardiopulmonary resuscitation (CPR) if breathing stops or heart stops beating. Medications, including: Epinephrine (adrenaline) to reduce your body's allergic response. Seek emergency treatment right away. In severe cases, untreated anaphylaxis can lead to death within half an hour. An antihistamine pill, such as diphenhydramine (Benadryl), isn't sufficient to treat anaphylaxis. These medications can help relieve allergy symptoms, but work too slowly in a severe reaction. Onset of anaphylaxis to stings or allergen injections is usually rapid: 70% begin in < 20 minutes and 90% in < 40 minutes. Food/ingestant anaphylaxis may have slower onset or slow progression. But they occurred in only 6% of anaphylaxis of mixed causes and are uncommon with insect stings. The ability of epinephrine to treat the many signs of anaphylaxis is rather amazing. It acts on a number of receptors in the body to exert its effects. First, it causes constriction, or tightening, of the blood vessels, which decreases swelling and also helps to increase blood pressure. Epinephrine 1:1,000 dilution, 0.2 to 0.5 mL (0.2 to 0.5 mg) in adults, or 0.01 mg per kg in children, should be injected subcutaneously or intramuscularly, usually into the upper arm. The site may be gently massaged to facilitate absorption. The dose may be repeated two or three times at 10 to 15 minutes intervals. Anaphylaxis is a potentially life threatening, severe allergic reaction and should always be treated as a medical emergency. When injected, adrenaline rapidly reverses the effects of anaphylaxis by reducing throat swelling, opening the airways, and maintaining heart function and blood pressure. Epinephrine acts on beta-2 receptor sites of smooth muscles in the airways. Glucagon works by stimulating higher cAMP levels and overrides the alpha and beta receptors so that epinephrine does not require those receptor pathways to work. Glucagon has documented positive inotropic and chronoscopic effects on the heart. Although histamine is involved in anaphylaxis, treatment with antihistamines does not relieve or prevent all of the pathophysiological symptoms of anaphylaxis, including the more serious complications such as airway obstruction, hypotension, and shock. Anaphylaxis can occur within minutes – the average is around 20 minutes after exposure to the allergen. Symptoms may be mild at first, but tend to get worse rapidly.

Typical symptoms and signs may include: Facial swelling, including swelling of the lips and eyelids. Some reactions can occur after several hours, particularly if the allergen causes a reaction after it has been eaten. In very rare cases, reactions develop after 24hours. Anaphylaxis is a sudden and severe allergic reaction that occurs within minutes of exposure. An anaphylactic reaction can occur within seconds of exposure and usually begins within a short time of the exposure to the allergen, but can be delayed up to two hours. It is important to note that anaphylaxis can occur without hives or other skin symptoms.

Atropine and isoproterenol have been inconsistent in reversing the bradycardia and hypotension of beta-blocker overdose. Glucagon increases heart rate and myocardial contractility, and improves atrioventricular conduction. This suggests that glucagon's mechanism of action may bypass the beta-adrenergic receptor site. For oral dosage form (capsules): Adults and teenagers—60 milligrams (mg) two times a day as needed or 180 mg once a day. Children 6 to 11 years of age-30 mg twice a day as needed. In these cases, OTC or prescribed antihistamines such as diphenhydramine (Benadryl) may help reduce symptoms. These drugs can be taken after exposure to an allergy-causing food to help relieve skin redness, itching, or hives. However, antihistamines cannot treat a severe allergic reaction. Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes more than one of the following: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure. These symptoms typically come on over minutes to hours. A shot of a drug called epinephrine is needed immediately, and you should call 911 for emergency medical help. The terms

"anaphylaxis" and "anaphylactic shock" are often used to mean the same thing. They both refer to a severe allergic reaction. Anaphylactic shock is shock that's caused by anaphylaxis. he most common signs and symptoms of an allergic reaction include: Cough difficulty or irregular breathing, wheezing, itchy throat or mouth, and difficulty swallowing, Nausea, vomiting, abdominal pain, and diarrhea, Itchiness, red bumps or welts on the skin (hives), and skin redness.

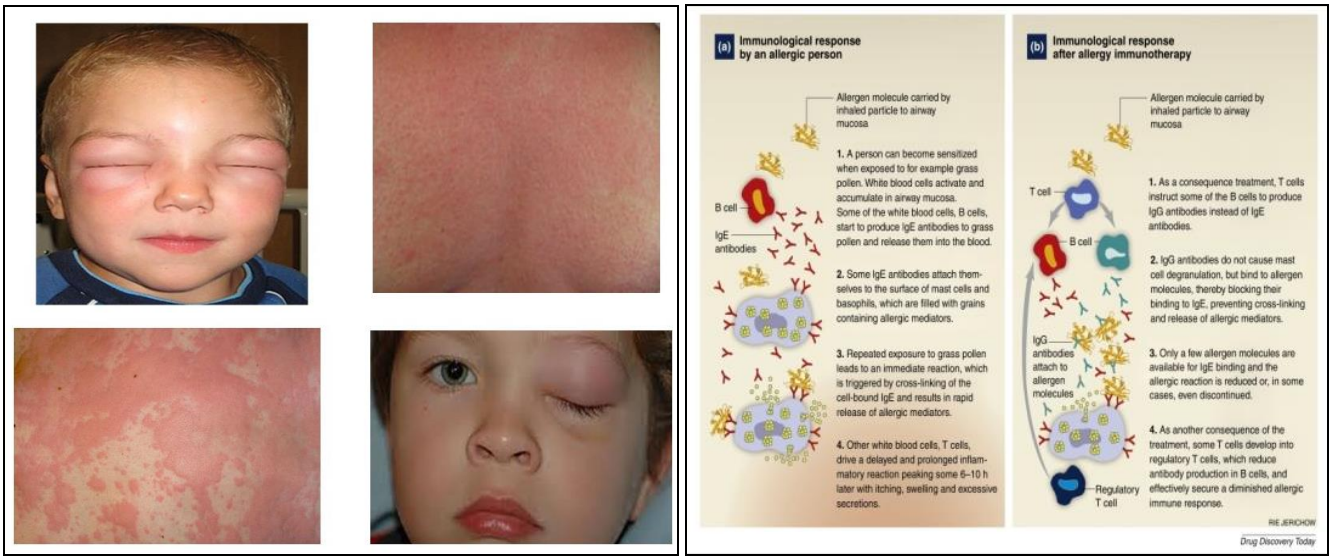


Fig 2

But sometimes, exposure to an allergen can cause a life-threatening allergic reaction known as anaphylaxis. This severe reaction happens when an over-release of chemicals puts the person into shock. Allergies to food, insect stings, medications and latex are most frequently associated with anaphylaxis. Seek emergency treatment right away. In severe cases, untreated anaphylaxis can lead to death within half an hour. An antihistamine pill, such as diphenhydramine (Benadryl), isn't sufficient to treat anaphylaxis. These medications can help relieve allergy symptoms, but work too slowly in a severe reaction. The primary drug treatments for acute anaphylactic reactions are epinephrine andH1 antihistamines. According to the 2013 World Allergy Association update, 2015 Joint Task Force anaphylaxis update, and 2010 NIAID guidelines, epinephrine is the drug of choice for life-threatening reactions. The ability of epinephrine to treat the many signs of anaphylaxis is rather amazing. It acts on a number of receptors in the body to exert its effects. First, it causes constriction, or tightening, of the blood vessels, which decreases swelling and also helps to increase blood pressure. Epinephrine 1:1,000 dilution, 0.2 to 0.5 mL (0.2 to 0.5 mg) in adults, or 0.01 mg per kg in children, should be injected subcutaneously or intramuscularly, usually into the upper arm. The site may be gently massaged to facilitate absorption. The dose may be repeated two or three times at 10 to 15 minutes intervals. No. EpiPen® or EpiPen Jr® and Mylan's authorized generics should only be injected into the middle of your outer thigh (upper leg), through clothing if necessary. Do not inject into your veins, buttocks, fingers, toes, hands or feet.

Diagnosis

History: the diagnosis of anaphylaxis relies principally on the history, including the time course of the event, such as history of exposure to a particular trigger, the time course between exposure and development of symptoms, and the evolution of symptoms and signs over minutes to hours. Diagnostic criteria: the diagnostic criteria set forth by the National Institutes of Health (NIH) in 2006 were based on three clinical scenarios: First, in the absence of an allergen, anaphylaxis is diagnosed by a rapid onset (minutes to hours) of a reaction that involves the skin, mucosal tissue, or both, alongside at least one of the following symptoms: respiratory compromise, reduced blood pressure, or symptoms of end organ dysfunction. Second, after a likely allergen exposure, two or more of the following occur: involvement of the skin or mucosal tissue, respiratory symptoms, decreased blood pressure, and/or gastrointestinal involvement. Third, in the case of a known allergen, reduced blood pressure alone is sufficient for the diagnosis of anaphylaxis [1]. Laboratory test: elevated serum tryptase levels can be detected within 15 minutes and up to 3 hours after the anaphylactic episode [2]. Levels greater than 11.5 ng/mL are considered elevated. Serum tryptase levels are rarely increased in the absence of shock or when food is the trigger [6]. Baseline elevations of serum tryptase levels should prompt consideration of the diagnosis of systemic mastocytosis [2, 4]. A recent consensus document defined a significant acute elevation of serum tryptase to be equal to or greater than 1.2 times the baseline +2 ng/mL, indicating likely mast cell activation [2, 5].

Treatment

In most instances, epinephrine can be administered intramuscularly. The dose in an adult is 0.3 to 0.5 cc. The standard intramuscular dose is a 1:1,000 concentration. This should be given in the lateral aspect of the thigh by

intramuscular injection. Adrenaline (sometimes called epinephrine) is given by injection to treat a life-threatening allergic reaction called anaphylactic shock. When adrenaline stimulates these receptors this causes the blood vessels to narrow, which stops the blood pressure from falling too low. When the dose is delivered and EpiPen ® is released from the injection site, the orange needle cover will automatically extend and immediately locks in place. The effects of epinephrine may wear off after 10 or 20 minutes. Epinephrine, more commonly known as adrenaline, is a hormone secreted by the medulla of the adrenal glands. Strong emotions such as fear or anger cause epinephrine to be released into the bloodstream, which causes an increase in heart rate, muscle strength, blood pressure, and sugar metabolism. The maximum tolerated dose of subcutaneously injected epinephrine has been estimated to be 7 to 8 mg. The minimum lethal human epinephrine dose by subcutaneous injection has been estimated to be 4 mg. However, survival was reported after 50 mg of adrenaline administered subcutaneously [6All published guidelines clearly identify epinephrine as the first-line medication for the treatment of anaphylaxis [1, 6]. Epinephrine 1:1000 (1 mg/mL) at a dose of 0.2–0.5 mg in adults and 0.01 mg/kg in children up to a maximum of 0.3 mg dosage should be used [6]. Injection in a large muscle, usually the lateral thigh, results in better absorption of the medication [2, 6]. There are currently two commercially available doses of epinephrine autoinjectors in the United States: 0.15 mg (ideal for a 15 kg body weight) and 0.3 mg (ideal for a 30 kg body weight). In Europe, a third dose of 0.5 mg has been marketed but is not available for use in the US. It is common practice to prescribe the 0.15 mg dose to children weighing as low as 10 kg and the 0.3 mg dose to children after they reach a body weight of 24 kg. The practice parameters allow physicians to use epinephrine every 5–10 minutes and even at shorter intervals if deemed necessary [6]. It is important to remember that patients on oral or even ophthalmic beta-blockers might not adequately respond to epinephrine [2, 7]. In these patients, isotonic saline and intravenous glucagon given at a dose of 1–5 mg in adults and 20–30 µg/kg in children, up to a maximum of 1 mg, should be given, followed by an infusion at a rate of 5–15 µg/minute titrated to clinical response [2, 3]. Depending on the setting (healthcare versus at home), intravenous fluids should be initiated to maintain adequate circulation [2, 3]. Another important consideration, which is often ignored, is to position the patient in the Trendelenburg position (lying flat on the back with legs elevated) in order to allow blood flow to the heart and to prevent the "empty ventricle syndrome" described by Pumphrey [3, 4]. Other supportive measures could be considered as second-line therapy. These include oxygen use, H1 and H2 antihistamines for the treatment of hives, and albuterol for the treatment of bronchospasm. We recommend using a non-sedating antihistamine as opposed to the common practice of prescribing diphenhydramine, as the sedative effect might obscure possible central nervous system symptoms. Corticosteroids are not useful for the acute treatment of anaphylaxis but may be effective in preventing biphasic or protracted anaphylaxis. As a result, many centers will administer a single dose of systemic corticosteroids (orally or intravenously) after the patient has been stabilized [5, 6]. A prolonged 3 or 5 day course is not indicated. The frequency of occurrence of biphasic reaction has been reported to be from as low as 1% to as high as 23% [6, 7]. These different estimates are likely due to varying definitions of anaphylaxis and the criteria used to identify a biphasic reaction. Using the NIH definitions for anaphylaxis in a retrospective chart review of two urban academic hospitals in Canada, Grunau *et al.* reported the incidence of a biphasic clinically important reaction to be 0.18% [9]. Currently, expert consensus recommends observation in the emergency room for a period of at least 6 hours after stabilization, 3, 8. Patients should be discharged home with a prescription for an epinephrine autoinjector (EpiPen), along with instructions for self-administration and a referral to an allergy/immunology specialist for diagnosis and prevention.

Prevention

Long-term preventive measures include the recognition and management of risk factors for anaphylaxis in general, as well as measures directed to the specific triggers in particular. It is important to identify and manage comorbid conditions that increase the risk of a severe anaphylactic reaction when poorly controlled. These include asthma, cardiovascular disease, and mastocytosis or mast cell activation syndrome. Furthermore, administration of certain medications such as beta-blockers may interfere with the therapeutic response to epinephrine as previously mentioned. Young children may not be able to recognize and report early symptoms of anaphylaxis, leading to a delay in administration of epinephrine. Adolescents and young adults often display risky behavior with regards to food avoidance and poor compliance in carrying the epinephrine autoinjector.

Food-induced anaphylaxis

Avoidance of the confirmed food trigger requires lifelong vigilance, including education on reading food labels, informing family and friends, and caution while eating in public establishments. Given the difficulty in implementing complete food avoidance and the resultant negative effect on quality of life, clear and consistent information should be provided regarding the specific food triggers. In some patients, food challenges performed in a clinical setting may be necessary to assess the clinical significance of positive skin tests or serum IgE levels. Various forms of immunotherapy for food desensitization are currently being investigated, including oral, sublingual, and patch application [1]. Primary prevention of peanut allergy in high-risk infants with severe eczema and/or egg allergy was recently reported in a landmark study where early introduction of peanut between the ages of 4 and 11 months in infants with negative oral peanut challenge resulted in a rate of peanut allergy of 3% at 5 years of age compared to 17% in the group of infants who practiced peanut avoidance, an 86% relative risk reduction in infants with negative peanut skin tests [2].

Medication induced anaphylaxis

As with foods, an accurate determination of the offending medication is needed. In situations when the patient is receiving multiple medications simultaneously a detailed history is crucial. Standardized skin testing is available for

penicillin only [3], although many protocols have been reported for other antibiotics and miscellaneous drugs [5, 4]. Once identified, the offending medication should be avoided and alternative therapies used. In that respect, it is important to identify medications with potential cross-reactivity to the offending agent. If no alternative medication is adequate to treat the underlying condition, careful desensitization by administering incremental doses of the offending drug can be performed, often in an intensive care unit setting [5, 7]. This procedure does not confer long-term tolerance to the drug, so future administration of the drug would once again require a desensitization procedure.

Insect sting anaphylaxis

Anaphylaxis to insects occurs in 3% of adults and 0.4–0.8% of children who are stung [6. History, as always, is key in identifying the insect, correlating the onset of symptoms to the sting event and helping in avoidance of future stings. Different insects build nests in different places: hornets build large nests in trees, yellow jackets in the ground, and wasps under houses or barns. Honeybees usually leave a stinger and build nests in tree hollows. Wasps, yellow jackets, and hornets are scavengers and are likely to be encountered in picnic areas where food is available. Fire ants build their nests in soil and often sting in a circular pattern multiple times. Patients with a history of insect sting hypersensitivity should be educated on avoidance of stings, carry an epinephrine autoinjector, and obtain a consultation with an allergist/immunologist in order to undergo specific serum IgE testing and skin testing to identify the culprit insects. Randomized controlled trials have demonstrated the development of long-lasting protection against anaphylaxis in most patients who are treated with subcutaneous venom immunotherapy for a period of 3–5 years [6]. Venom extracts are available for honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp, and whole body extract is available for fire ant. Patients with mastocytosis and mast cell activation syndrome have an increased risk of anaphylaxis with insect sting, whereby the anaphylactic episode could be the presenting sign of the disorder [6, 3].

Exercise induced anaphylaxis

EIAn, as the name implies, is anaphylaxis induced by physical activity. The mechanism behind it is still not entirely clear. Symptoms usually start within a few minutes after exercise and include fatigue, flushing, itching, and urticaria. If exercise continues, symptoms may progress in severity with angioedema of the airways and death [5]. Often, a co-trigger is required for symptoms to develop, such as a specific (or any solid) food, NSAIDs, menstruation, alcohol, or even pollen exposure in sensitized individuals [1, 6]. The risk of anaphylaxis with exercise may occur within 4–6 hours of food and alcohol ingestion and within 24 hours after administration of NSAIDs. The most common food trigger in the USA is wheat, followed by grains and seafood [15]. Potential co-triggers could be identified through skin testing and exercise challenge testing despite its low sensitivity. It is imperative to identify the co-triggers in order to provide education on avoidance. H2 antagonists should be avoided, as preliminary data show that they might interfere with the normal digestion of food and potentially lead to a more severe reaction [6, 7]. Therefore, prevention is individualized to the patient and to the co-triggers. These patients can exercise regularly once the co-trigger is avoided for a period of time prior to exercise. They should be counseled to exercise with a partner at all times and should carry epinephrine for autoinjection. If early signs or symptoms develop, the patient should stop exercising in order to avoid progression [6].

Allergy to galactose-alpha-1,3-galactose, also known as "alpha-gal".

More recently, a new cause of anaphylaxis has been linked to red meat consumption with a delayed onset of 3–5 hours or more after ingestion [6, 8]. Patients usually report a history of a lone star tick bite 1–3 months prior to anaphylaxis. The pathogenesis is due to the development of an IgE response to a mammalian oligosaccharide epitope, galactose-alpha-1, 3-galactose, known as alpha-gal, present in the tick and conserved in mammalian meat [7]. A typical presentation would be a patient waking up in the middle of the night and collapsing on the way to the bathroom after ingestion of mammalian products for dinner. Episodes are sporadic [7]. There is a commercially available serum test to detect IgE against alpha-gal. Avoidance of mammalian meat is recommended as well as availability of an epinephrine autoinjector.

Idiopathic anaphylaxis

Idiopathic anaphylaxis remains a diagnosis of exclusion after extensive history and testing to rule out specific triggers, including foods, exercise, medications, and insect hypersensitivity. Laboratory workup to look for evidence of mast cell activation is indicated. Serum tryptase levels obtained at baseline, as well as within 3–4 hours of an acute episode, can be helpful in demonstrating acute mast cell activation [2, 5]. Other mast cell mediator measurements of urinary metabolites include N-methylhistamine, leukotriene E4, and prostaglandin F2 alpha (PGF2alpha). An elevated basal serum tryptase level suggests the diagnosis of systemic mastocytosis. A bone marrow biopsy can also be considered [7, 1]. In patients with elevated serum PGD2 (or its urinary metabolite, PGF2alpha), treatment with 650 mg aspirin twice a day is recommended [2, 3]. Treatment with high-dose prednisone, 60–100 mg daily for 1–2 weeks along with non-sedating H1 and H2 antihistamines, followed by tapering the dose of prednisone on alternate days over a period of 3 months has also been shown to decrease the frequency and severity of anaphylactic episodes, but results in high toxicity [7, 5]. Multiple reports [7, 8], as well as our own experience, have shown that treatment with omalizumab, a monoclonal anti-IgE antibody, can lead to decreased frequency of episodes and is very well tolerated. An epinephrine autoinjector should be carried at all times.

Conclusion

Anaphylaxis is a potentially life-threatening condition. Given its high prevalence, 2–5% of the population, physicians of all specialties are likely to be tasked with the recognition and management of anaphylactic episodes. In this regard, several consensus guidelines, including the American, European and

World Allergy Organization guidelines, have been published to facilitate this task [1-3]. A careful history and specialized testing to identify potential triggers are paramount in preventing future events. Measurements of mast cell mediators in biologic fluids can improve the diagnostic accuracy of anaphylaxis. Epinephrine remains the mainstay of treatment for acute episodes. Emerging therapies include the use of omalizumab as well as allergen-specific immunotherapy.

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