

Summation anaphylaxis: A challenging diagnosis

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Abstract

Anaphylaxis is the most severe of allergic reactions. The most frequent triggers of anaphylaxis in childhood are food, insect venom, drugs, exercise, etc. In some cases, the presence of more than one trigger is necessary for the allergic reaction, while one trigger alone is tolerated. This rare condition is called summation anaphylaxis (SA). Food-dependent exercise-induced anaphylaxis is the most well-known SA. However, SA may also occur with the association between food and/or exercise plus one or more of the following other cofactors, such as drugs, especially non-steroidal anti-inflammatory (NSAID), alcohol, infections, temperature variation, and menstrual cycle. SA can explain some cases of idiopathic anaphylaxis, as well as cases of an apparent breakdown in a previously acquired tolerance for food, or finally, when faced with a suggestive clinical history of food allergy or exercise anaphylaxis and the provocation test is negative. In these situations, a more careful clinical history looking for other cofactors is necessary.

KEYWORDS

anaphylaxis, cofactors, food-dependent exercise-induced anaphylaxis, summation anaphylaxis

Anaphylaxis is defined as "a serious, life-threatening generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death".¹ The most frequent triggers of anaphylaxis in childhood are food, insect venom, and later, drugs. Less frequent causes are exercise, latex, immunotherapy, vaccines, and very rarely the cold and menses. In most cases, anaphylaxis is due to only one of the factors listed above. In some cases, however, the presence of two or more triggers is required for the allergic reaction to occur, while one allergen alone is tolerated. This

rare condition is called summation anaphylaxis (SA).² Even if many triggers may contribute to its development, this seems to occur only if food or exercise is one of the factors. SA can explain some cases of idiopathic anaphylaxis, as well as cases of an apparent breakdown in a previously acquired tolerance for food, or finally, when faced with a suggestive clinical history of food allergy or exercise anaphylaxis and the provocation test is negative.

Allergic reactions and anaphylaxis are mainly due to mast cells, basophil activation, and the immediate release of preformed

mediators, such as histamine and various proteases and later a release of cytokines, chemokines, and other mediators. Immune cell activation may be achieved either by an IgE-dependent mechanism, where an allergen-specific IgE complex binds to the high-affinity IgE receptor or by a non-IgE-dependent mechanism.³ The mechanisms that lead to the amplification and generalization of an allergic reaction are numerous and largely unknown.

It is possible to speak about SA even when the presence of one or more cofactors produces a more severe allergic reaction or when anaphylaxis can occur at lower doses of the allergen. Clinical studies have suggested several cofactors: food, exercise, drugs, alcohol, infections, cold and hot temperatures, and hormonal factors. These cofactors are present in anaphylaxis in 30% of adults and 18% of children.⁴ It is not well known how these cofactors may facilitate an anaphylactic reaction. It has been hypothesized that they may increase allergen bioavailability in allergic reactions by increasing gut permeability, thereby facilitating IgE production. Other hypothesis include: lowering the thresholds for basophils and mast cells activation, alterations in plasma osmolality and pH, blood flow redistribution and increased tissue transglutaminase activity.

The most frequent SA is the food-dependent exercise-induced anaphylaxis (FDEIA). People affected by FDEIA have no reaction after eating food or doing exercise alone, but they may have anaphylactic reactions if these two elements occur together. FDEIA may be classified as non-specific food-dependent exercise-induced anaphylaxis (nsFDEIA) and specific food-dependent exercise-induced anaphylaxis (sFDEIA).

nsFDEIA is a rare condition: The first case report, from Kidd et al,⁵ described an athlete presenting with anaphylaxis 2 hours after a meal. He was not sensitized to food allergens, and he could eat every kind of food without any problems. If he fasted, he could do all sorts of strenuous exercise without any reaction. Despite these observations, any kind of meal taken before doing sport seemed capable of triggering anaphylaxis. Only a few other cases have been described subsequently.

sFDEIA is far more common and occurs in food-sensitized patients who generally have mild or no symptoms after ingestion of those specific foods.⁶ A wide variety of foods such as cereals, vegetables, fruit, seafood, milk, and cheese can induce sFDEIA. Wheat, in particular, the omega-5 gliadin allergen (Tri a 19), is the main food responsible for FDEIA in Japan and European countries. In most cases, symptoms occur when food is ingested from a few minutes to 2 hours before exercise, but there are also reports of reactions to food ingested up to 6 hours before exercise. sFDEIA usually occurs after submaximal exercise lasting from a few minutes to 1-3 hours, such as running, playing, or even in less intense exercise. It seems that the more intense the exercise, the greater the risk of a more severe reaction, regardless of the food involved.

SA may also be due to the association between food and drugs, especially non-steroidal anti-inflammatory drugs (NSAID), food and alcohol, food and infections, or between exercise and NSAID, exercise, and temperature changes, and, finally, hormonal changes.

Key message

When the cause of anaphylaxis remains unknown, it is necessary to consider summation anaphylaxis.

NSAIDs are important cofactors for food anaphylaxis; they are involved in more than 22% of sFDEIA cases, and over 58% are in the Mediterranean area. They could lead to anaphylaxis, together with various allergens (eg, with lipid transfer proteins). In wheat-dependent exercise-induced anaphylaxis (WDEIA), even a small amount of acetylsalicylic acid may cause anaphylaxis in 84% of cases when associated with wheat. In some children, taking aspirin along with wheat, even without physical activity, was enough to trigger anaphylaxis.⁷

According to one study, the combined intake of alcohol and gluten may cause anaphylaxis in 11% of cases, and it may also reduce the reaction threshold for anaphylaxis after wheat ingestion in 37% of cases.

Infections are cofactors in 1.3%-11% and 2.5%-3% of anaphylactic reactions in adults and children, respectively. A study showed that half of the patients had anaphylaxis during cow's milk, and egg oral desensitization and exercise and infections were the most common cofactors.

Among NSAID, acetylsalicylic acid (ASA) is the most frequent cofactor involved in the exercise-induced anaphylaxis (EIA). In the first description of EIA, five out of 16 patients had ingested ASA before exercise. Other studies have confirmed this association. Van Wijk⁸ described the case of a child with a clinical history of anaphylaxis during exercise after taking naphylpropion acid (Naprosyne®), a non-steroidal anti-inflammatory drug. An exercise challenge test confirmed the diagnosis after Naprosyne intake.

Several observations suggest that the association between exercise and temperature changes may also induce SA. Sayama described a case of cold-dependent exercise-induced anaphylaxis. A 16-year-old Japanese boy had a 4-year history of recurrent wheezing and dyspnoea after physical exercise in winter. Only a provocation test with the combination of exercise and cold stimulation elicited the reaction. Moreover, in a study of 279 patients with EIA, 44% of them reduced the incidence of attacks by avoiding exercise during extremely hot or cold weather.⁹

In some cases, SA occurs with the association of 3 cofactors, such as food, exercise, and NSAID. In other cases, as many as 4 cofactors were needed. Bito¹⁰ reported the case of a girl who had exercise anaphylaxis following the intake of milk, but the OFC with milk, exercise, and even ASA could not reproduce the reaction. However, a reaction did occur when repeating the OFC during the ovulatory phase. Thus, the menstrual cycle also seems to be a trigger for anaphylaxis and a cofactor for the development of SA. Little is known about the mechanism by which hormones can contribute to the development of anaphylaxis. Regarding hormonal factors, the increase in progesterone that occurs during the menstrual cycle has been implicated in the so-called catamenial anaphylaxis.

In conclusion, the diagnosis of food or exercise-induced anaphylaxis needs to take a careful history, skin allergy testing, laboratory investigations, and appropriate food or exercise challenges. However, when an appropriate diagnostic process results inconclusive, it would be necessary to suspect SA.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Mauro Calvani: Conceptualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Fabio Decimo:** Writing-review & editing (equal). **Anania Caterina:** Writing-review & editing (equal). **Enza D'Auria:** Writing-review & editing (equal). **Violetta Mastroianni:** Writing-review & editing (equal). **Angelica Santoro:** Writing-review & editing (equal). **Elisabetta Veronelli:** Writing-review & editing (equal). **Marco U. A. Sartorio:** Writing-review & editing (equal). **Giovanni Cosimo Indirli:** Writing-review & editing (equal). **Barbara Cuomo:** Writing-review & editing (equal).

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