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CASE REPORT

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Appearance of food-dependent exercise-induced anaphylaxis as an inflammatory disease: a pediatric case report and differential diagnosis

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Abstract
Anaphylaxis is the most serious of all allergic reactions. Despite advances in the knowledge of anaphylaxis, its clinical manifestations continue to be under-recognized. Indeed, proper diagnosis of anaphylaxis is often missed, and the treatment is delayed. The underlying causes are still under investigation globally. Inflammation represents the cornerstone of pathophysiology of anaphylaxis. Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare clinical manifestation characterized by a chronological sequence in which food ingestion followed by physical exercise leads to anaphylaxis. Its mechanisms are yet to be fully explained. We report the case of a 14-year-old Chinese male who lost consciousness while undergoing physical activity at school. Several differential diagnoses were considered such as hypovolemic shock, septic shock, anaphylactic shock or neurological adverse event. Finally, the diagnosis of FDEIA was made. This case highlights the difficulties in diagnosing FDEIA and its management, especially when the clinical history is not complete and detailed.

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Introduction

Anaphylaxis is a severe, life-threatening, generalized hypersensitivity reaction[1]. Most episodes of anaphylaxis occur in the public. The lifetime prevalence of anaphylaxis is estimated at 0.05–2% in the United States and about 3% in Europe.[2] Despite advances in its knowledge and awareness even outside the healthcare settings, its clinical manifestations continue to be under-recognized. Indeed, the diagnosis of anaphylaxis is often missed, and the treatment is often delayed. Intramuscular adrenaline is the medication of choice as the first aid treatment of anaphylaxis.[3] Its delayed administration is associated with poor outcomes, including higher fatality rates.[3] The most common triggers of anaphylaxis in children are food allergens.[4] Other possible underlying causes are still under investigation globally.

Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare clinical condition in which anaphylaxis occurs during (or soon after) exercise, always preceded by causative food ingestion.[5] FDEIA is an uncommon condition in children, being mainly reported as case reports or case series.[5] Data on the prevalence of FDEIA in childhood are scarce.[5] Any food could trigger FDEIA, although it depends on the geographical area.[5] Its pathophysiology is yet to be elucidated. Making a diagnosis of FDEIA is challenging and must rely on a detailed clinical history and rigorous diagnostic algorithm. The diagnosis of FDEIA has important implications for the patient's life, because it helps to avoid potentially dangerous foods and allows a safe return to physical exercise.[5]

Case Report

We report the case of a 14-year-old Chinese boy. Although he was born in Italy and grew in China, he returned to Italy at the age of 8 years. He was severely obese (weight 120 kg; BMI 39) but had no other underlying disease. While performing an exercise during the physical education lesson at school (he was walking briskly), he began to feel dizzy. He suddenly experienced aphasia, blurred vision, and sphincter relaxation, and after a few minutes, he lost consciousness for a few seconds. His pulse and breath were present, and the teacher put him in the lateral safety position. When emergency medical services arrived, he had tachypnea, shortness of breath, and low peripheral blood oxygen saturation (86%) without oxygen support. He also had mild hypotension and tachycardia, with blood pressure (BP) of 100/70 mmHg and a heart rate of 150 beats per minute. His Glasgow Coma Scale (GCS) score was 14. He was transferred to the nearest hospital, supported by an oxygen mask with a reservoir bag.

Despite high-concentration oxygen flux, he had shallow breathing with poor lung ventilation at the emergency department. His clinical examination revealed hypotension (BP 95/65 mmHg), delayed capillary refill time (CRT; about 5 s), hypothermia, and a diffused erythematous skin rash. His state of consciousness was fluctuating, alternating between drowsiness and deep agitation. Therefore, he was sedated with intravenous (i/v) midazolam (5 mg) and supported with a high-concentration oxygen bag mask. Invasive BP monitoring and massive intravenous fluid therapy with Ringer lactate solution was started. Blood tests showed respiratory acidosis, neutrophilic leukocytosis, and a slight increase in serum creatinine (1.26 mg/dL) and procalcitonin (PCT) 2.38 ng/mL, with negative C-reactive protein (CRP). Transaminases were normal. Timeline of results of blood test is shown in Table 1.

With the suspicion of significant bleeding (e.g., intracranial, thoracic, or splanchnic), a complete head-neck-thorax-abdomen computed tomography (CT) scan was performed. No abnormalities were detected except for a collapsed inferior vena cava, suggestive of hypovolemia.

Further investigations, including electroencephalography (EEG), electrocardiography (ECG), and echocardiography, were performed. They showed normal findings, excluding main neurological or cardiac adverse events, as several differential diagnoses were taken into consideration. Clinical conditions and vital signs did not improve despite massive intravenous fluid administration. No major

Table 1 Blood test results during hospitalization.

			10 AM	12 PM*	6 PM	8 AM	8 AM	8 AM	8 AM
	MU	NV	HD1	HD1	HD1	HD2	HD3	HD6	HD9
White blood cells (WBC)	n./uL	3500–14,000	15,410	-	17,820	16,120	-	8250	7680
Neutrophils (N)	%	25–65	88%	-	93.5%	84%	-	68.9%	60.8%
C-reactive protein (CRP)	mg/dL	<0.5	0.3	-	4.57	5.43	2.47	1.04	0.48
Procalcitonin (PCT)	ng/mL	<0.5	2.38	-	17.8	-	-	1.23	0.25
Troponin T HS (TnT)	pg/mL	<14	-	-	581	413	434	127	-
NT-proBNP	pg/mL	5–207	-	-	392	252	364	34	-
Creatine phosphokinase (CPK)	UI/L	39–308	-	-	21,681	11,571	5946	544	164
Lactate dehydrogenase (LDH)	UI/L	10–260	-	-	1263	729	-	-	312
Aspartate aminotransferase (AST)	UI/L	5–32	42	-	266	211	153	-	46
Alanine aminotransferase (ALT)	UI/L	5–18	28	-	113	108	112	83	84
Creatinine (Cr)	mg/dL	0.5–0.9	1.26	-	0.9	0.74	-	0.81	0.76
Tryptase	ug/L	-	23	-	-	-	-	-	1

AM: ante-meridian; HD: hospitalization day; MU: measurement units; NV: normal values; PM: post-meridian.
*Intramuscular administration of adrenaline (0.5 mg, twice) and intravenous hydrocortisone (100 mg) and chlorphenamine (10 mg).

cause of fluid loss was detected, excluding primary hypovolemia. Therefore, causes of distributive shock were considered. Suspecting septic shock because of the slight rise in serum PCT, intravenous antibiotic therapy with ceftriaxone (2 g) was started but without significant improvement of clinical conditions. By exclusion, idiopathic anaphylaxis was considered, and intramuscular adrenaline was administered twice (0.5 mg per dose). Intravenous hydrocortisone (100 mg) and chlorphenamine (10 mg) were also administered. After about 20 min, clinical conditions began to improve. His breathing returned to normal, and his lung ventilation improved as well. Peripheral blood oxygen saturation was at 95% with a Venturi oxygen mask (volumetric flow rate: 4 L/min; and fraction of inspired oxygen: 28%). His BP was 130/75 mmHg, and his CRT almost normalized. He was transferred to our tertiary care hospital.

When he arrived at our pediatric ward, he was eupneic, and his peripheral blood oxygen saturation was at 97% without oxygen support. His BP and CRT were normal. His neurological examination was unremarkable. Blood tests showed neutrophilic leukocytosis with elevated inflammatory markers (CRP 4.57 mg/dL and PCT 17.8 ng/mL). Antibiotic therapy with ceftriaxone (2 g twice a day) was continued. Muscular, myocardial, and hepatic cytolysis markers were also increased (creatine phosphokinase 21,681 UI/L, lactate dehydrogenase 1263 UI/L, troponin T 581 pg/mL, aspartate aminotransferase 266 UI/L, and alanine aminotransferase 113 UI/L; see Table 1).

Since the first EEG was performed in an urgency regimen under sedation, the second complete sleep-awake EEG was performed, which showed normal brain electrical activity. A complete cardiac evaluation was repeated: the echocardiography was normal; only minimal changes in ventricular repolarization were detected. Broad-spectrum infectious disease investigations on the patient's blood and stool (with cultures and polymerase chain reaction [PCR] methods) were performed, which presented negative results.

During the patient's hospitalization, his cytolysis markers normalized gradually (Table 1). Timeline of patient's clinical course is shown in Figure 1.

After 5 days of hospitalization, we tried to understand in a better manner about what had happened before and during the episode with the help of a native Chinese interpreter because of language difficulties. Through a more detailed clinical history, other remarkable details became evident. The boy recalled a sensation of flushing, itchy neck, and shortness of breath before losing consciousness. Furthermore, he revealed having eaten breakfast with a slice of pizza about 60 min before the episode. Moreover,

	CLINICAL ONSET	FIRST AID (911)	HOSPITAL			
	9.30 AM	9.45 AM	10.00 AM	12.00 PM	12.30 PM	2.00 PM
A		airways at risk	airways at risk		patent airways	patent airways
B		tachypnoea	shallow breathing		eupneic	normal lung ventilation
		SpO_2 86%			SpO_2 95% (VM: 4L/min, FiO_2 28%)	SpO_2 97% without oxygen
C		HR 150 bpm	BP 95/65 mmHg		BP 130/75 mmHg	BP 135/90 mmHg
			CRT 5 seconds		CRT 3 seconds	CRT 2 seconds
		BP 100/70 mmHg	central and peripheral SBP present		central and peripheral SBP present	central and peripheral SBP present
D	weakness dizziness blurred vision lost of consciousness	GCS 14	drowsiness alternating with deep agitation		GCS 15	GCS 15
E		cold sweating	BT 35° C		BT 37° C	BT 37° C
			erythematous skin rash		no skin rash	no skin rash
TREATMENT		oxygen	oxygen sedation ventilation IV fluids antibiotics	oxygen IM adrenaline IV hydrocortisone IV chlorphenamine	oxygen	

Figure 1 Timeline of patient's clinical course. A: airway; AM: ante-meridian; B: breathing; BP: blood pressure; BT: body temperature; C: circulation; °C: degree celsius; CRT: capillary refill time; D: disability; E: exposure; FiO_2: fraction of inspired oxygen; GCS: Glasgow Come Scale; HR: heart rate; IM: intramuscular; IV: intravenous; PM: post-meridian; SBP: systolic blood pulse; SpO_2: peripheral blood oxygen saturation; VM: Venturi mask.

the result of serum tryptase (taken at first admission) was available; it was deeply increased (23 mcg/L), suggesting the possible diagnosis of anaphylaxis.

Hence, an allergological evaluation was performed: skin prick tests (SPTs) with commercial extracts of milk, egg, fish, tomato, peanut, soy, wheat, and inhalants (i.e., *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Phleum pretense, Alternaria alternata, Parietaria judaica, Artemisia vulgaris, Betulla spp., Cupressus spp.*, cat and dog dander, and *Olea europea*) (Lofarma, Milano, Italy) showed a weak positivity for *Dermatophagoides pteronyssinus*. According to the current standards, histamine 10 mg/mL (Lofarma, Milano, Italy) and normal saline were used as positive and negative control substances, respectively. That's why, the specialist at first hypothesized idiopathic anaphylaxis based on clinical presentation, significant improvement after intramuscular adrenaline administration, and elevated serum tryptase in the acute phase. Because the patient ate a slice of pizza about 1 h before the episode, despite negativity of SPT for wheat, this allergen remained a strongly suspected trigger. The patient's clinical history was further investigated. He had reported having several episodes of urticarial skin rashes after eating pizza in the past, always occurring about 2 h after the ingestion and while performing mild physical exercise (i.e., walking). He never had similar episodes when he ate wheat derivatives and did not indulge in exercise afterward. The allergy diagnostic work-up was therefore deepened: total serum immunoglobulin E (IgE) was mildly increased (255 kU/L; normal values: 0–100 kU/L); wheat-specific IgE (sIgE) level was mildly increased (0.52 kUA/L; normal values: 0–0.1 kUA/L), both determined using a commercial assay (ImmunoCAP System, Thermo Fisher Scientific, Uppsala, Sweden). Main molecular wheat allergens (Tri a 14, Tri a 19) dosage was requested. Basal serum tryptase was also repeated 9 days after the admission, showing normal values (1 mcg/L).

The patient was trained to use an auto-injectable adrenaline device in case of similar episodes; he was advised to avoid any potential food trigger from 4 h prior to 1 h after doing exercise. He was discharged in complete health with the diagnosis of idiopathic anaphylaxis.

At the first allergological follow-up, the immuno-solid phase allergen chip (ISAC test; Thermo Fisher Scientific) was performed to investigate a broader spectrum of potential causes of anaphylaxis. Results showed moderate to high IgE positivity (6.8 International Standardized Units [ISU-E]) for wheat lipid transfer protein (LTP) Tri a 19 (omega-5 gliadin). Thus, the wheat-dependent exercise-induced anaphylaxis (WDEIA) diagnosis was finally established.

Discussion

Multisystem involvement is a milestone in the clinical presentation of anaphylaxis. Itchy skin rashes, altered mental status, shortness of breath, hypotension, and tachycardia are among the most typical clinical features.[6,7] Our patient initially presented with dizziness, blurred vision, and sphincter relaxation. These symptoms, despite being less common, may also be the clinical manifestations of anaphylaxis.[7] A more detailed subsequent investigation of the clinical history revealed the presence of itch and dyspnea. This challenging case highlights the difficulties in diagnosing anaphylaxis, especially when skin rash is not present or unreported at clinical onset.

First, major bleeding and serious adverse cardiac or neurological events were excluded. Since clinical conditions did not improve after massive rehydration, causes of distributive shock were subsequently considered. Consistent with neutrophilic leukocytosis and a mild increase in PCT, septic shock was hypothesized, and antibiotic treatment was initiated immediately.

Procalcitonin is one of the markers with the highest specificity for infection;[8] however, it increases in many other critical conditions, such as trauma, myocardial infarction, pancreatitis, autoimmune disorders, severe organ dysfunction (e.g., renal failure), and malignancy as well as in neonates.[9] Furthermore, PCT has been described as elevated in systemic inflammatory response syndrome (SIRS) of noninfectious origin.[10,11] Anaphylaxis is not routinely considered a cause of SIRS; however, increasing evidence in the scientific literature has shown association between elevated PCT levels and anaphylaxis.[12,13]

The generalized inflammation occurring during anaphylaxis results from different mechanisms, including IgE- and IgG-mediated reactions, cytokine release, contact system activation, complement-mediated reactions, and direct mast cell or basophil activation.[14]

Food allergens usually trigger IgE-mediated reactions.[14] They are classically caused by an allergen binding to a specific IgE, which in turn binds to the high-affinity receptor for IgE (FcεRI) on mast cells and basophils, leading to their activation and subsequent release of multiple inflammatory mediators, for instance, histamines, tryptase, platelet-activating factors, nitric oxide, leukotrienes, chymase, prostaglandins, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, and other cytokines.[14] TNF-α induces the autocrine expression of nuclear factor kappa B (NF-κB) in mast cells. This transcription factor promotes the expression of IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which amplify inflammatory cascade through the recruitment of eosinophils, neutrophils, and macrophages.[14] PCT release from thyroid C cells and neuroendocrine cells scattered throughout the human body is mediated by IL-6, TNF-α, and IL-1β. These increased cytokines during anaphylaxis could therefore be responsible for PCT elevation.[14,15]

Exercise-induced anaphylaxis (EIA) is a form of physical allergy in which exercise precipitates anaphylaxis attacks. In 1979, Maulitz et al. reported the first case of FDEIA, which occurred when the ingestion of food (shellfish) preceded exercise by 5 h.[16] Since then, several patients of FDEIA have been reported, and this entity, although still rare, has been thoroughly studied.

Physical exercise is well known to function as a stress factor during and after its execution, leading to inflammation.[17] Type, intensity, duration, and familiarity of training have been shown to regulate a complex inflammatory cascade occurring after acute physical exercise.[18,19] The variable expression of pro-inflammatory cytokines after training is thought crucial for long-term adaptive responses to physical exercise.[20]

Therefore, the combination of physical exercise with other stress factors (such as exposure to food allergens close to training) could facilitate and enhance inflammatory response.[21]

Our patient underlines the relevance of clinical associations while interpreting laboratory test results. Clinicians must always be aware of alternative causes of elevation of PCT. Fortunately, intramuscular adrenaline was administered quickly, although anaphylaxis was only suspected. Subsequent profound clinical improvement suggested that such diagnostic suspicion was well-founded.

A biochemical hallmark of inflammation during anaphylaxis is represented by tryptase. The serum levels of tryptase, a serine protease stored in human mast cells and basophils, often rise during anaphylaxis because of the degranulation of mast cells. For this reason, it is currently considered a helpful marker to diagnose anaphylaxis if taken between 30 min and 4 h of acute episode.[22] The correct timing of serum tryptase dosage is, therefore, mandatory. In our case, serum tryptase dosage was performed about 1 h after the clinical onset; its elevated serum level in combination with the normal level outside the acute phase supported the diagnostic suspicion, even if normal values may also be found during anaphylaxis.[22]

Another interesting feature of anaphylaxis is represented by myocardial injury; however, its causes are yet to be clearly understood. Massive systemic vasodilatation may lead to sudden coronary hypoperfusion. However, myocardial injury can also be due to anaphylaxis itself. This condition is known as Kounis syndrome, defined as a hypersensitivity coronary disorder constituted by the association of an acute coronary syndrome with a hypersensitivity, allergic, anaphylactic, or anaphylactoid reaction with four different types.[23,24] Another discussed possible mechanism for myocardial injury is the coronary vasospasm secondary to the therapeutic doses of epinephrine for anaphylaxis.[25,26] Our patient only showed an initial increase in myocardial cytolysis markers, which quickly normalized without any clear clinical, electrocardiographic, or echocardiographic signs. Establishing a definite cause of myocardial damage during anaphylaxis is always challenging, and different mechanisms may overlap. However, clinicians must always be aware of possible cardiac adverse events in the setting of anaphylaxis.

In managing suspected idiopathic anaphylaxis,[27] the importance of good history-taking should not be forgotten. The presence of possible triggers and cofactors should be carefully and repeatedly investigated.[28] A few days after the event, with the help of a Chinese interpreter, our patient revealed that wheat was a potential trigger; subsequent physical exercise acted as a cofactor. As first-level diagnostic tests resulted negative, second- and third-level investigations were therefore deemed necessary.

The ISAC array is increasingly considered a useful tool in the clinical practice of allergy, especially in the diagnostic work-up of idiopathic anaphylaxis.[29] The main strength of microarray technology is that many allergens can be studied in a single test. A potential limitation lies in the difficulty of interpretation in multiple positivity when a convincing clinical history is not present. In our patient, the ISAC test revealed a relevant sIgE positivity for the wheat LTP Tri a 19 (omega-5 gliadin). In a multicenter study carried out in the United Kingdom, omega-5 gliadin was identified as one of the allergens most frequently involved in unrecognized sensitizations, accounting for 45% of patients, together with shrimp.[30] In this study, the ISAC test led to a definitive diagnosis in 20% of patients with idiopathic anaphylaxis. Thus, multiplex IgE arrays can provide additional information that may help to address diagnostic shortcomings.

After ISAC results, given the history of wheat intake about 1 h prior to the episode, the diagnosis of FDEIA was finally established. FDEIA is a rare subset of anaphylaxis with a growing incidence.[31] The age of onset of FDEIA is usually adolescence,[32] probably because physical activity does not occur at preplanned intervals in children.

In 1998, a Japanese study showed that the prevalence of FDEIA among children attending junior high school was 0.017%.[33] The same study was repeated in 2012, showing a comparable prevalence (0.018%), despite a better knowledge of this condition.[34] In 2018, another Japanese study showed a significantly lower prevalence (0.0047%) of FDEIA among elementary school children.[35] Intensity of physical exercise among elementary school students is usually lower than their counterparts of junior high school; this could be one of the possible reasons for these different findings.[35] However, the prevalence of FDEIA is probably underestimated in these studies because of the lack of awareness of this disease among school staff.[35]

Causative foods of FDEIA differ by the country.[32] Tomatoes, wheat (in particular the omega-5 gliadin allergen), and peanuts are the most frequently suspected foods in a large Italian cohort,[36] whereas in Japan, wheat and shrimp have been reported as common causative foods.[37,38] However, it should always be kept in mind that any food could trigger FDEIA.

Regarding the pathophysiology of FDEIA, it is still unclear why hypersensitivity occurs only after a combination of food intake and physical activity. The main working hypotheses involve changes in plasma pH, osmolarity and mast cell degranulation threshold, altered tissue enzyme activity, increased gastrointestinal permeability, facilitated epitope recognition, and allergen binding.[39]

In the setting of WDEIA, *in vitro* and *in vivo* studies showed that tissue transglutaminase (tTG)-mediated cross-linking of omega-5 gliadin peptides may enhance their IgE binding capacity.[40] During physical exercise, activation of tTG in the intestinal mucosa usually occurs through IL-6 release, leading to the formation of large allergen complexes able to trigger anaphylactic reactions.

Diagnosing FDEIA can often prove challenging. First, a rigorous clinical history must be collected, focusing on potential food triggers, their quantity, and the time relationship between food ingestion, physical exercise, other potential cofactors, and the allergic reaction.

In the diagnostic work-up of food allergy, *in vivo*, SPT, and serum-specific IgE are the first-line tests to assess sensitizations, even if negative results do not rule out food as a culprit.[41] Oral food challenge still represents the gold standard for diagnosing food allergy[41] and FDEIA.[37] This test can be performed as an open food challenge or a double-blind placebo-controlled food challenge.[41] However, these procedures are rarely performed in clinical practice because of their potential risk of anaphylaxis.[42]

In our case, the patient had a severe allergic reaction during physical exercise, and wheat was almost the only suspicious food trigger. Therefore, considering the isolated IgE positivity for omega-5 gliadin that emerged from the ISAC array, the oral food challenge was considered inappropriate because of its low risk-benefit ratio.

Intramuscular administration of adrenaline is a critical treatment in the management of FDEIA.[41] Patients who have experienced FDEIA must avoid any potential food triggers at least 4 h prior to and 1 h following physical exercise. They must be trained to use auto-injectable adrenaline and instructed to always carry their emergency plan with them. In such patients, a gradual return to physical exercise is recommended, better if under medical guidance.[5,43] An elimination diet is not necessary; on the contrary, a gradual reintroduction of trigger foods is advisable.[5,43]

Conclusion

Clinicians must always be aware that anaphylaxis may be a possible cause of PCT elevation; it should always be considered in patients of suspected distributive shock with elevated inflammatory markers. Furthermore, prompt serum tryptase dosage during acute phase is of primary importance to support the diagnostic suspicion of anaphylaxis.

This case highlights the difficulties in diagnosing FDEIA and its management, especially when the clinical history is not complete and elaborated. FDEIA is a rare condition in which a combination of ingested food and physical exercise leads to the onset of anaphylaxis. Its mechanisms are yet to be fully understood. Further rigorous studies are required to clarify how the physiological changes occurring during physical activity, intensity of physical exercise, and timing of food ingestion might elicit anaphylaxis. Proper diagnosis of FDEIA results in important and positive implications for the patients' safety and quality of life.

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Conflict of interest

The authors declared not to have any conflict of interest.

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