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Literature review

Idiopathic anaphylaxis

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ABSTRACT

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion when no cause can be identified. As with other forms of anaphylaxis, IA is life-threatening. Its prevalence is difficult to determine and the mechanism is not clearly understood. Investigation of a suspected case of idiopathic anaphylaxis involves 3 steps. First, objective criteria are sought to establish the diagnosis of anaphylaxis; next, differential diagnoses are ruled out; finally, screening for hidden allergens is performed. The aim of this approach is to reduce the chance of false negative diagnosis of IA. The management of acute reactions is no different than for any case of anaphylaxis. When symptoms are seen frequently, prophylactic therapy is required to prevent attacks. There is no standard long-term prophylaxis for IA. The prognosis is generally favourable. IA patients should be regularly re-evaluated since certain newly recognized aetiologies may account for some situations, as with α -gal allergies and mast cell disorders.

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R É S U M É

L'anaphylaxie idiopathique est un diagnostic d'exclusion, évoqué lorsque l'élément déclenchant n'est pas identifié. Comme dans toute forme d'anaphylaxie, l'AI peut mettre en jeu le pronostic vital. La prévalence est difficile à estimer et les mécanismes physiopathologiques ne sont pas bien connus. L'investigation d'une AI doit passer par trois étapes : tout d'abord la recherche de critères objectifs pour établir le diagnostic d'anaphylaxie, puis l'élimination des diagnostics différentiels, et finalement la recherche d'allergènes cachés. Cette approche a pour but de réduire les faux diagnostics d'IA. La prise en charge des réactions aiguës ne diffère pas de celle des anaphylaxies classiques. Quand les manifestations se répètent, des traitements préventifs de crises peuvent être initiés, même s'il n'existe pas de prophylaxie standardisée. Le pronostic est en général favorable. Les patients pour lesquels le diagnostic d'IA a été porté devraient être réévalués régulièrement. Certaines étiologies de découverte récente pouvant expliquer des réactions, comme ce fut le cas pour les allergies à l' α GAL ou la mastocytose.

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1. Introduction

Anaphylaxis is defined as a “severe, life-threatening systemic hypersensitivity reaction” [1].

It is characterized by its rapid onset, with potentially life-threatening airways, breathing or circulatory problems. It is

usually, but not always, associated with skin or mucosal changes [2].

Common key triggers involve food, drugs and stinging insects, but in some cases the trigger cannot be identified, despite detailed clinical evaluation. This special form of anaphylaxis, known as idiopathic anaphylaxis (IA), is a diagnosis of exclusion. It requires careful assessment of the clinical history of the episode, skin tests, and measurement of specific serum IgE levels to identify potentially hidden allergens and, if necessary, a graded challenge [3].

The first description of IA dates to 1978, when several cases were reported in the United States. However, since the 1990s, similar

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cases have been reported in numerous other countries world-wide [4].

2. Epidemiology

The distribution of anaphylaxis-eliciting triggers in Europe was estimated in the Network of Severe Allergic Reactions (NORA) study in 2014. Food, insect venom and drugs are the main triggers of anaphylaxis, but their relative importance varies with age and geographic location.

The current incidence and prevalence of idiopathic anaphylaxis is difficult to determine since it depends on who is performing the diagnosis. The Network of Severe Allergic Reactions in Europe reports the lowest number of cases of IA (6.5%), but the data used were collected by a network that is highly specialized in allergy diagnosis [5].

Greenberger estimates that IA accounts for around 30% to 60% of cases of anaphylaxis in adults and for some 10% of such cases in children [6].

As with other forms of anaphylactic reaction, fatalities can occur in IA [7].

Although the incidence of anaphylaxis has been increasing in recent years, according to a recently published report, the frequency of IA appears to be decreasing. The relatively recent discovery of a new allergen, an IgE-mediated antibody response to alpha-gal, as a cause of anaphylaxis, may offer an explanation for this decrease [8].

According to most reports, while IA can occur in both males and females, it is more common in females after puberty and until menarche. Several studies have observed that over 60% of cases are seen in females [9] in this age group.

While IA was first reported among adults, subsequent reports have shown that it can affect subjects of all ages, although it remains less common in children [5,10].

There is a high prevalence of atopy in patients with IA, with a rate of 59% being seen in one case series [11].

3. Possible pathogenic mechanisms

Many theories posited to explain IA, supported by clinical and experimental studies, have failed to find a pathogenic mechanism underpinning IA.

Lymphocyte activation has been observed in IA patients compared with normal patients. Using flow cytometry analysis, Grammer et al. found that during acute episodes of IA, patients exhibit significant increases in T cell activation markers compared with control groups. However, IA patients also have more activated B cells, both during acute episodes and at baseline, compared with control patients [12]. Given the higher incidence of IA in females, researchers investigated whether oestrogen or progesterone affected basophil activation in patients with suspected hormone-related IA. However, no differences in basophil activation were observed between this group and controls [13].

Another hypothesis is that T cells in IA result in polarization towards a Th2 response, with production of aberrant cytokine (IL-4, IL-5 and IL-13) able to lower the threshold for mast cell degranulation [3].

Despite the above hypotheses, an IgE-mediated response by a trigger that remains unidentified could be the main mechanism underpinning IA.

3.1. Clinical manifestations

The manifestations of IA are identical to those that occur during anaphylaxis with known triggers and depend on the organs

Table 1

History-keeping for the reaction.

<i>History of the reaction</i>
Onset
Description of symptoms
Grade
Duration
Treatment
Emergency-room record
Tryptase level
<i>Cofactors</i>
Exercise
Alcohol
Drugs
In females, menstruation cycle
Infection
Stress

involved. The Sampson criteria (Table 1) demonstrate excellent sensitivity (96.7%) and good specificity (82.4%) for the diagnosis of anaphylaxis [2].

They should therefore be used by physicians to identify possible cases of idiopathic anaphylaxis.

The first episode of IA is usually the most severe. A typical episode is acute in onset and reaches a peak anywhere between minutes and a few hours.

In a series of 335 patients with IA, all had experienced angioedema and urticaria. Isolated cardiovascular collapse was not reported in this case series [14].

4. Allergological work-up

4.1. Assessing the diagnosis of anaphylaxis

A detailed history of the reaction is needed to confirm a diagnosis of anaphylaxis according to the Sampson criteria. Consequently, isolated urticaria or angioedema cannot be considered as anaphylaxis. The reaction must be of rapid onset. It is also very important to record the duration of the event, as well as the recurrence of symptoms after initial resolution. Details of the treatment of the reaction must also be recorded, such as use of epinephrine or attendance of an emergency department. Review of emergency-room records and acute serum tryptase measurements are invaluable in determining objective signs of anaphylaxis.

Cofactors that might have exacerbated the reaction must also be checked. Exercise, alcohol, oestrogens, and drugs such as NSAIDs, ACE inhibitors, β -blockers and lipid-lowering drugs are the chief factors to be considered, although their mechanisms and signalling pathways remain poorly understood [15].

4.2. Ruling out differential diagnoses

The ruling out differential diagnoses are:

- flushing may be a sign of anaphylaxis if accompanied by other signs. However, many conditions can lead to flushing: hormonal causes (carcinoid syndrome, neuro-endocrine tumour, vasoactive intestinal peptide tumour, pheochromocytoma, medullary thyroid cancer); pharmacological causes: vasodilator drugs, niacin; cutaneous causes: rosacea; neurological causes: dysautonomia; psychological causes: emotions; physiological causes (heat, exercise), food intake (spicy food), mast cell activation;
- vocal cord dysfunction;
- severe acute asthma exacerbation;
- hereditary (HEA) and acquired angioedema (AAE) can both be life-threatening and can mimic anaphylaxis, because of possible prodromal symptoms such as erythema marginatum, and

Table 2
WHO criteria for systemic mastocytosis.

WHO criteria for systemic mastocytosis	
Major criteria	Multifocal, dense aggregates of mast cells (15 or more) detected in sections of bone marrow and confirmed by tryptase immunohistochemistry or other special stains
Minor criteria	Bone marrow biopsy showing ≥ 25% of mast cells in the infiltrate with atypical morphology (spindle-shaped, clusters) KIT-positive mast cells co-express CE117 with CD2 and/or CD25 Detection of KIT point mutation at codon 816 in bone marrow, blood or other organs Serum total tryptase persistently > 20 ng/mL

Table 3
Modified REMA Score.

Variable	Score
Gender	
Male	+1
Female	−1
Clinical symptoms	
Absence of urticaria, pruritus and angioedema	+1
Urticaria, pruritus and/or angioedema	−2
Presyncope and/or syncope	+3
Tryptase	
<11.4 ng/mL	−1
>20 ng/mL	+2

because of the association with abdominal pain or diarrhoea, but the most ominous symptoms are related to the airways, with oedema of the oropharynx and larynx, which may lead to airway obstruction. Whereas IA is acute and short-lasting, HEA worsens over approximately 1.5 days and lasts for 2–5 days [16];

- histamine (scombroid) fish poisoning: this results from ingestion of histamine-contaminated fish such as mackerel, bonito, albacore and skipjack tuna, but also non-scombroid fish, such as sardine, bluefish and, more rarely, salmon. Occasionally, cheeses, particularly Swiss cheese, have been involved. Scombroid poisoning occurs when fish are inadequately frozen, allowing bacteria to thrive and then convert histidine to histamine. If other people eating at the same restaurant also fall ill the likely cause is histamine fish poisoning [17];
- cholinergic urticaria potentially leading to life-threatening multisystem reactions. In this case, cholinergic triggers, such as raised body temperature or strong emotions, lead to anaphylaxis symptoms. Cutaneous involvement is present in almost every case [18];
- clonal mast cell disease (systemic mastocytosis or monoclonal mast cell activation syndrome). A study evaluating 30 patients previously diagnosed with idiopathic anaphylaxis noted that 12 of the 30 patients showed evidence of clonal mast cell disease [19]. However, in contrast to IA, patients with clonal mast cell disease do not usually have accompanying urticaria or angioedema. In addition to a skin infection, mast cell infiltration may also occur in bone marrow, liver, spleen and the gastrointestinal tract. Systemic mastocytosis is defined by the presence of at least 1 major WHO criterion and 1 minor WHO criterion or 3 minor WHO criteria, as shown in Table 2. Patients with only one or two minor criteria pertaining to mast cell clonality qualify for diagnosis of monoclonal mast cell activation syndrome [20];
- the REMA scoring system uses combined clinical and laboratory parameters to predict underlying MC clonality in patients presenting with systemic mast cell activation symptoms including anaphylaxis. A REMA score ≥ 2 is the most reliable cut-off value to predict mast cell disease [21] (Table 3);
- a modified version of the scoring system has now been established with a baseline serum tryptase cut-off value of

11.4–20 ng/mL, and this has resulted in greater sensitivity and specificity [19];

- in the case of subjective symptoms, a somatoform disorder should of course be suspected: panic attacks, experiencing globus hystericus (Table 4).

4.3. Screening for hidden allergens

Screening for triggers requires keeping a comprehensive history.

The responsibility of common allergens must be eliminated: a detailed history of substances within the 6 h prior to the event is thus needed. This includes details of any food eaten together with ingredients thereof, but also drinks, food eaten by other people, food present in the same location, and food cooked, in order to rule out inhaled allergens. Medications, including non-prescription drugs, and inhaled medications must be evaluated, as well as any related stings or bites.

The location is important in identifying a trigger (country, indoors, outdoors, home, work), as is the time of year and time of day.

Contact with latex objects must be evaluated.
Contact with cannabis must also be evaluated since several anaphylactic reactions to cannabis have been reported, whether through inhalation, ingestion or cutaneous contact [22].

Information on the activity in which the patient was engaged at the time of the event and of any contact with furry animals can also help reveal a trigger. Several cases of anaphylaxis resulting from contact with horses have been described [23] (Table 5).

4.3.1. Focus on suspicion of food allergy

According to European data from the network of severe allergic reactions (NORA), food is involved in 64.9% of reactions in children and 20.2% of reactions in adults. Post-prandial anaphylaxis should thus undergo detailed investigation to determine the food responsible [5].

Hidden allergens may have been used as an ingredient in food or result from contamination or infestation. Our way of eating has changed over recent decades. With globalization, we are continually being exposed to new foods, many meals eaten are composite meals, and new health habits have ushered in new food trends, such as the replacement of wheat and milk. These changes increase the potential number of allergens, some of them being due to cross reactivity with the known allergens of subjects, as is the case for fenugreek or lupin with known allergy to peanuts. Isabel Skypala has proposed a list of common hidden allergens and associated foods [24].

There is also a growing trend towards inclusion of seeds in diets. Sesame appears to be the most common seed responsible for hypersensitivity reactions, but anaphylaxis also occurs with other seeds that may be hidden allergens [25].

Food additives are rarely suspected in anaphylaxis, but they should nevertheless be considered if the patient reports a history of reactions with numerous foods or to a certain food when it is commercially prepared but not when it is home-made, and where the assessment has ruled out allergy to a major food ingredient [26].

Increasingly, food products are also being used in complementary medicine. The main products that have been observed to elicit anaphylaxis are *Andrographis paniculata*, different species of *echinacea*, bee products, *Ginkgo biloba*, ginseng and *psyllium* and *ispaghula* [27,28].

The French allergy vigilance network registers severe allergic reactions declared by allergists. A review of emerging allergens together with previous lists provides a precious tool in helping prepare an allergy work-up, as shown in Table 6.

Table 4
Differential diagnosis with clinical symptoms and diagnostic tests.

Disease	Clinical symptoms									
	Flush	Urticaria	Pruritus	Globus hystericus	Angioedema	Stridor	Swallowing difficulties	Dyspnoea	Respiratory distress	Wheezing
Cholinergic urticaria	+	++	++	+	+++	++	++	++	++	++
Vocal cord dysfunction		-	-	-	-	++	+	+	+	-
Severe acute asthma exacerbation	-	-	-	-	-	-	-	+++	+++	+++
Scombroid poisoning	++	+	+	+	+	+/-	+/-	+	+	+
Hereditary and acquired angioedema	Erythema marginatum	-	-	+	+++	++	+++	+++	++	-
Carcinoid syndrome or tumours	+	-	-	-	-	-	-	+	+	+
Pheochromocytoma	++	-	-	-	-	-	-	-	-	-
Mast cell disorder	-	+/-	+/-	+/-	+/-	+/-	+/-	+	+	+
Somatoform disorder	+/-	-	++	++	-	+	++	++	+/-	-

Disease	Clinical symptoms							
	Abdominal pain	Diarrhoea	Vomiting	Dizziness	Palpitations	Head-ache	Presyncope	Syncope
Cholinergic urticaria	+	+	+	++	++		++	++
Vocal cord dysfunction	-	-	-	-	-	-	-	-
Severe acute asthma exacerbation	-	-	-	-	-	-	+	+
Scombroid poisoning	++	++	+	+	++	++	+	+
Hereditary and acquired angioedema	++	++	++	-	-	-	-	-
Carcinoid syndrome or tumours	+/-	+	-	-	-	-	-	-
Pheochromocytoma	+	++	-	-	++	++	-	-
Mast cell disorder	+	+	+	+	++	-	++	++
Somatoform disorder	++	-	-	++	++	++	++	-

Disease	Diagnostic tests		Laboratory outcome	
Cholinergic urticaria	None			
Vocal cord dysfunction	Laryngoscopy			
Severe acute asthma exacerbation	Respiratory Function tests			
Scombroid poisoning	Histamine levels in the fish		>50 mg of histamine per 100 g of fish	
	Skin prick to prick with suspected fish and with non-suspected fish		Positive only with suspected fish	
Hereditary and acquired angioedema	C4- C1-INH level functional and quantitative		Low C4 (<10 mg/dL) C1-INH depends on type	
Carcinoid syndrome or tumours	Serum serotonin 24-h urinary; 5 hydroxyindolacetic acid		>400 ng/mL >15 mg/24 h	
	Serum chromogranin A Vasoactive intestinal peptide		>36.4 ng/mL >200 pg/mL	
	Serum calcitonin		>8 pg/mL (women) or > 16 pg/mL (men)	
Pheochromocytoma	24-h urinary fractionated catecholamines		Norepinephrine > 1005 nmol/d; epinephrine > 191 nmol/d; dopamine > 4571 nmol/d	
	24 h urinary metanephrine Plasma fractionated metanephrine		1.3 mg/24 h Metanephrine > 0.5 nmol/L; normetanephrine > 0.9 nmol/L	
Mast cell disorder	Serum tryptase Urinary histamine metabolites Urinary 11βPGF2α Urinary prostaglandin D2 KITD816V mutation		20 ng/mL Elevated from baseline Elevated over baseline Elevated over baseline Positive	
Somatoform disorder	Bone marrow biopsy Corticosteroid test		See criteria Ineffective	

Adapted from Carter M.

4.3.2. An allergy to food may not be to the food itself

Hidden allergens can also include those present due to contamination or infestation, such as cereal mites, which are frequently present in pancakes, in other flour containing foods but also in cheese, ham, chorizo and salami.

Anisakis simplex is a parasite that can infect fish, such as cod and salmon.

Insects can also accidentally be present in foods [24].

4.3.3. Food allergens may be present in non-food items

Santoro et al. reported reactions with medicinal products in which lactose has become contaminated with milk protein. Such medicinal products may include dry powder inhalers or methylprednisolone sodium succinate 40 mg injection [30].

In one case, a child's fingerprint test kit containing wheat provoked anaphylaxis in a boy with a wheat allergy [31].

Table 5
Elements of history-keeping in IA.

Context of the reaction
Food ingested within the 6 h before the event
Drinks
Food ingested by other people, food cooked
Medications including non-prescription drugs, inhaled medications, complementary medicine
Stings or bites
Location: country, indoors, outdoors
Contact with latex
Contact with cannabis products
Kissing or sexual intercourse
Activity in which the patient was engaged at the time of the event
Contact with animals
Previous known food allergies
Air temperature

4.3.4. Anaphylaxis occurring during the night

Cases of anaphylaxis awaking a patient or occurring during the night are rarely seen, but in such cases, it is important to seek to identify a specific culprit.

Of course, delayed anaphylaxis due to red meat being eaten for dinner by patients sensitive to alpha-gal must also be considered. In a prospective study of 70 participants referred with a diagnosis of idiopathic anaphylaxis (IA), Carter et al. found that 6 (9%) had IgE to alpha-gal. Following implementation of a diet free of red meat, none of the patients had any further episodes of anaphylaxis [32].

In certain countries, insect bites can also lead to nocturnal anaphylaxis. In western and southern regions of the United States, in Mexico and in Central and South America, members of the *Triatoma* species, also called kissing bugs, have been reported to cause allergic reactions in people living in homes that have cracks or crevices in the walls and thatched roofs [33].

In Europe, *Argas reflexus* is a tick that feeds on urban pigeons, but it may also bite humans. The key characteristics are severe anaphylactic reactions occurring at night during spring and summer as well as the presence of pigeons in the immediate vicinity [34].

In 2003, Fritz et al. described asthma and allergic rhinitis in buckwheat allergic patients due to buckwheat pillows. These pillows, also known as sobakawa pillows, have become more popular with the trend towards using more natural materials and, with the increasing occurrence of buckwheat allergies, could lead to nocturnal anaphylaxis [35].

Relationships with other people and any intimate behaviour has to be checked, since anaphylaxis to food or drugs can be kiss-induced and allergens can be transmitted during sexual intercourse. Latex allergy must also be considered. Hypersensitivity reactions to human seminal fluid have also been reported [36,37].

5. Physical examination

High blood pressure is a criterion for differential diagnosis (pheochromocytoma). The examination should focus on urticaria pigmentosa, classically described as salmon-coloured macules that urticate upon stroking (Darier's sign), suggesting cutaneous mastocytosis.

6. Diagnostic tests

A skin prick test or specific IgE test for suspected allergens should be performed. For food allergens, sensitization should be related to the symptoms and, if necessary, an oral challenge should be carried out in a safe environment.

Systematic skin prick tests can be a useful tool to evaluate hidden allergens. In 1986, Stricker et al. proposed a battery of 79

food skin prick tests for 102 patients initially diagnosed with IA. Thirty-two patients were sensitized to 1 or more foods; 7 were considered allergic to these foods and 10 different allergens were found to be responsible for anaphylaxis: aniseed, cashew nut, celery, flaxseed, hops, mustard, mushroom, shrimp, sunflower and walnut [38].

When a food allergen is suspected and cofactors are present, sensitization to LTP (a ubiquitous protein in vegetables) should be sought.

A useful device for revealing a patient's IgE antibody profile is an advanced tool known as ImmunoCAP ISAC. This is a miniaturized immunoassay platform in which allergen components are immobilized in a microarray. Thus, in one study, ISAC was able to show evidence of sensitization to newly identified allergens in 20% of an IA cohort. The link between these new sensitisations and anaphylaxis was considered to be "highly likely". The main drawback of this study was that an allergen challenge procedure was not performed; hence some cases may have been merely sensitized [39].

Newly identified aetiologies, such as a food allergy to galactose- α -1.3-galactose and mastocytosis, should first be researched. Following this, differential diagnoses of IA should be eliminated. Table 7 summarizes the most likely symptoms of these diagnoses and their diagnostic tests.

7. Management of IA

7.1. Management of an acute reaction

There is no difference between the management of an acute reaction and of any other form of anaphylactic reaction. Training in the use of self-injectable epinephrine is essential, and should include recognition of signs of anaphylaxis, the correct epinephrine administration technique to be used, and how to contact emergency services.

All patients with idiopathic anaphylaxis should be advised to avoid taking drugs that might complicate treatment or worsen an event (beta blockers, ACE inhibitors, angiotensin blockers, monoamine oxidase inhibitors or MAOIs, and certain tricyclic antidepressants or TCAs such as amitriptyline) [6].

8. Maintenance therapy

When symptoms are observed frequently, prophylactic therapy is required to prevent attacks.

There is no standard long-term prophylaxis for IA.

The patient can be managed by administering prednisone in a non-continuous manner over one year. There have been reports of such treatment resulting in significant reductions in both the frequency and severity of IA. However, these patients may become corticosteroid-dependent, with the risk of long-term side effects from corticosteroids.

Daily H1 anti-histamines can be administered [40]. For prednisone-dependent patients, ketotifen, which also is a mast cell stabilizer, has been shown to be particularly effective in this regard [41].

If these medications fail to induce remission, alternative therapies should be considered, such as leukotriene antagonists [3,4,20].

Use of an anti-IgE monoclonal antibody, omalizumab, has proved effective in a few young patients with resistant IA at 300–375 mg every 2–4 weeks [9,42].

Rituximab, an anti-CD20 monoclonal antibody, resulted in complete remission in a 17-year-old patient with resistant IA [43]. These case reports are encouraging, but further studies are required to confirm the efficacy of these therapies.

Table 6
Hidden allergens and cross reactivity.

Hidden allergen	Food most likely to contain the hidden allergen	Potential cross reactivity
<i>Animal allergens</i>		
Goat milk	Cheese, yogurt	Cow's milk
Ewe milk	Cheese, yogurt	Cow's milk
Buffalo milk	Cheese: mozzarella – burrata	Cow's milk
Alpha-gal	Mammalian meat, pork kidney, gelatine, sweets	Mammalian meat
Snail	Prepared snails, soup	Shellfish–dust mites
Anisakis	Raw or marinated fish	
<i>Insect allergens</i>		
Mealworm	Flour	Crustaceans, house dust mites
Crickets		Crustaceans, house dust mites
Locusts		Crustaceans, house dust mites
<i>Plant allergens</i>		
Barley	Breakfast cereals, bread, biscuits	
Oat	Breakfast cereals, bread, biscuits	
Rye	Bread	
Buckwheat	Bread, French pancakes, noodles, gluten-free products	Hazelnut, wheat, sesame, soy, poppy seed, peanut, latex
Quinoa	Salads	Buckwheat
Celery	Industrially prepared soups, stir-fried vegetables, stock cubes, some cured meats, flavoured salts	
Pomegranates		
Moringa		
Yuzo		
Peanuts	Snacks, sauces, chocolates, biscuits	
Soy	Textured meat, vegan products, cakes (speculoos biscuits)	Leguminous plants: possible cross reactivity with peanuts
Peas	Vegan products, sausages (knacki), textured meat, biscuits, ice creams	Leguminous plants: possible cross reactivity with peanuts
Lupines	Flour, bread, cakes, beans eaten as a snack	Leguminous plants: possible cross reactivity with peanuts
Beans	Bread	Leguminous plants: possible cross reactivity with peanuts
Chickpeas	Hummus, salads	
Fenugreek	Mixed spices, curry powder, ras el hanout	Leguminous plants: possible cross reactivity with peanuts
Walnuts	Cakes, oil	
Cashew nut	Pesto sauce, chocolates (Cote d'Or praline), cheese, ravioli	
Mango	Fruit juice	Cashew nut
Pistachio	Yogurts, cakes, chocolate, snacks	Cashew nut
Pink peppercorn	Could be added as a garnish	Cashew nut
Sumac	Mediterranean dishes, Za'atar	Cashew nut
Pectin	Jams, jellies, desserts	Cashew nut
Citrus seeds	Fruit juice	Cashew nut
Hazelnut	Chocolates, biscuits, cakes	
Pecan nut	Biscuits, snacks, cheese (Boursin cheese: 3 nuts)	
Brazil nut	Snacks, breakfast cereals	
Macadamia nut	Snacks, ice creams	
Coconut	Chocolates, yogurts, ice cream, cakes	
Chestnut	Chestnut cream	
<i>Seeds</i>		
Sesame	Bread, snacks, Asian meal, tahini sauce, biscuits, chocolates, salads	Poppy seed, peanut, hazelnut
Mustard	Mayonnaise, vinaigrette, tart bases	
Pine nuts	Pesto sauce, salads, noodles, ready-to-eat meals	
Pumpkin seeds	Bread, salads, biscuits	Peanut, tree nuts, and other seeds
Flaxseed	Bread, salads, biscuits, cakes	
Poppy seed	Bread, biscuits, cakes	Hazelnut, sesame seed, rye, buckwheat, kiwi
Sunflower seed	Bread, biscuits, salads, cakes	Peanut, pistachio, brazil nut, poppy seed, artemisia, sunflower pollen
Goji berry	Breakfast cereals, salads, cakes, smoothies	
Millet seeds	Salads, bread, cakes	
Hempseed	Bread, salads, cakes, snacks	Cannabis
Amaranth seed	Bread, salads, cakes	
Chia seed	Bred, salads, cakes	Sesame seed
Spices	Ready-made dishes, some cured meats	
Cardamom		
Coriander		
Cumin		
Parsley		
Garlic		
<i>Dyes</i>		
Rocou Annatto	Orange colouring in cheese (Mimolette, Cheddar, Edam, Rouy), Chamonix biscuits... E160B	
Tartrazine	E102	
Cochineal red	E120, orange Tic Tacs, Campari	
Carmines red	E120	
Beetroot red	E162	
Paprika	E160C	
Locust bean, carob	E410 flavoured yogurts, ice cream (Magnum)	Leguminous plants: possible cross reactivity with peanuts

Table 6 (Continued)

Hidden allergen	Food most likely to contain the hidden allergen	Potential cross reactivity
Gums		
Guar gum	E412 ice cream (Magnum)	Leguminous plants: possible cross reactivity with peanuts
Tragacanth gum	E413	
Acacia gum	E414	
Xanthan gum	E415 certain milk-based desserts, sorbets	
Karaya gum	E416	
Sweeteners		
Thaumatococcus	E957 sweet-tasting protein, sweetener	
Brazzein	Sweet-tasting protein, sweetener	Cashew nut
Mabinlin	Sweet-tasting protein, sweetener	
Hive products		
Honey		
Royal jelly		
Pollen balls		
Bee or wasp larvae		
Mold or algae		
<i>Penicillium notatum</i>	Sausage or cheese rind	
<i>Fusarium venenatum</i> (mycoprotein)		
Complementary medicine products		
<i>Psyllium or ispaghula</i>		
Brewer's yeast, <i>Saccharomyces cerevisiae</i>		
Spirulina	Smoothie	
<i>A. paniculata</i>		
<i>Echinacea</i> species		
<i>G. biloba</i>		
Ginseng		

Modified from Baker et al. [29].

Table 7

Causes of nocturnal anaphylaxis.

Causes of nocturnal anaphylaxis	Context
Delayed anaphylaxis to alpha-gal	Red meat eaten at dinner
Bites from triatomine insects	In the Western and Southern United States, Central and South America
<i>A. reflexus</i>	Pigeons in the immediate vicinity
Buckwheat allergy	Buckwheat pillow
Latex allergy	Use of latex in condoms
Food or drug allergy	Sexual intercourse or kissing
Human semen allergy	Sexual intercourse

9. Prognosis

The prognosis of IA is generally favourable. In the studies reported to date, the overwhelming majority of patients achieve remission [10,14].

However, fatalities can occur with IA. In one case report, a patient with asthma was unable to take prednisone and suffered a fatal reaction to IA [44].

10. Conclusion

IA is a diagnosis of exclusion and requires a systematic evaluation to eliminate differential diagnoses. This allergological work-up is time-consuming and ambulatory hospitalization may be required to guarantee an exhaustive evaluation.

The hypotheses advanced regarding the mechanisms of IA have so far proved disappointing for allergists and IA patients should therefore be regularly re-evaluated, since newly recognized aetiologies may explain some situations, as has been found to be the case for α -gal allergies and mast cell disorders.

Disclosure of interest

The authors declare that they have no competing interest.

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