



Oral mite anaphylaxis: who, when, and how?

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Purpose of review

To present an update on the recent advances in the understanding of the mechanisms and practical management of oral mite anaphylaxis (OMA, pancake syndrome).

Recent findings

Among novel observations regarding OMA, this review highlights the increased prevalence of aspirin/NSAID hypersensitivity in patients affected by OMA, the association of OMA with exercise-induced anaphylaxis, the presentation of OMA simulating acute asthma, the occurrence of OMA in childhood, the high severity and lethal potential of OMA, the contamination of other foods, such as oat and corn flour with mites, and the simultaneous induction of OMA symptoms in more than one individual exposed to the same food source.

Summary

OMA is a severe, potentially lethal, acute allergic condition that should be suspected whenever symptoms begin soon after the intake of mite-contaminated foods. Physician awareness on this clinical picture is of paramount importance to establish a correct diagnosis and to implement adequate preventive measures to help patients at risk to avoid its occurrence.

Keywords

anaphylaxis, domestic mites, oral mite anaphylaxis, pancake syndrome, storage mites

INTRODUCTION

Various hidden allergens and contaminants present in the food may trigger clinical symptoms in selected patients soon after ingestion. Those include micro-organisms, toxins, chemicals, food additives, allergens from other foods, cross-reacting allergens from pollens (oral allergy syndrome), latex, and drugs. Anaphylaxis following the ingestion of mite-contaminated foods (oral mite anaphylaxis, OMA) was reported for the first time by Erben *et al.* in 1993 [1].

This syndrome is defined as the occurrence of severe symptoms resembling allergy immediately after eating foods containing mites. It has also been designated in the literature as the pancake syndrome, pancake anaphylaxis, and the new aspirin triad.

It is known that some foodstuffs are susceptible to be colonized by mites, including grain, oil seeds, dog feed, cheese, dried milk, and ham. However, foods prepared with wheat flour, and especially pancakes, have been incriminated more frequently, and therefore, the name of 'Pancake Syndrome' [2].

More than 200 patients with OMA have been reported from different locations, including Spain, Venezuela, Peru, Japan, United States of America, Brazil, Singapore, Belgium, Taiwan, Panama, Ireland, and Thailand. More often patients with OMA have

been observed in countries located in the intertropical region [3–5]. However, new cases have been recently reported from locations with temperate climate [6].

This article is an updated review of recent advances in the understanding of this new entity, its implications for patients and medical practitioners, and the unmet needs regarding its pathogenesis and practical management.

WHAT ARE THE CLINICAL MANIFESTATIONS OF ORAL MITE ANAPHYLAXIS?

OMA should be suspected in patients who show symptoms suggestive of an acute allergic reaction,

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KEY POINTS

- Oral mite anaphylaxis (OMA, pancake syndrome) is an acute severe reaction induced by foods contaminated with mites that is being increasingly recognized in many parts of the world.
- Wheat flour in pancakes is the most common food offender, although there are reports of OMA triggered by corn or oat flour.
- It affects atopic, mite-sensitive individuals of any age or sex.
- Thermoresistant allergens from both, domestic and storage mites can be involved.
- Prevention through a reduction of the time and temperature for storing of the flour is recommended, especially in locations with high environmental temperature and humidity.
- Increased physician awareness is required for early diagnosis, treatment, and prevention of this condition.

including respiratory (breathlessness, wheezing, cough, rhinorrhea, dysphonia, stridor, sneezing, cyanosis), cutaneous (angioedema, urticaria, skin rash, pruritus) cardiovascular (tachycardia), gastrointestinal (dysphagia, abdominal cramps, vomiting), symptoms beginning shortly after the intake of foods prepared with wheat flour.

Individuals of all ages can be affected [7], and no sex differences have been observed. In most cases, symptoms occur before 30 min after eating the incriminated food, and reactions are more often classified as severe or life-threatening (more than 75% of patients) [8].

Patients who develop OMA are atopic, having a previous medical history of rhinitis and/or asthma, and are sensitized to mite allergens, as confirmed by means of immediate-type prick skin testing or through the presence of mite-specific IgE in the serum [9].

Table 1 summarizes the clinical features and complementary investigations that can be employed for the diagnosis of OMA (see also Fig. 1).

WHAT ARE THE RISK FACTORS FOR THE DEVELOPMENT OF ORAL MITE ANAPHYLAXIS?

Among the clinical features that constitute a higher risk to present severe reactions to mite-contaminated foodstuffs, the following should be highlighted:

- (1) Previous atopic diseases.
- (2) Sensitization to domestic mite allergens.

Table 1. Oral mite anaphylaxis: diagnosis

1	Compatible symptoms after eating foods made with flour
2	Previous history of atopic diseases: rhinitis, asthma
3	Positive prick tests to mite extracts or presence of mite-specific IgE in the serum ^a
4	Positive skin tests to an extract of the incriminated flour ^a
5	Negative skin tests to commercial wheat extract ^a
6	Negative skin tests to an extract of uncontaminated flour ^a
7	Tolerance to foods made with uncontaminated flour
8	Microscopic identification of mites in the incriminated flour
9	Presence of mite allergens in the incriminated flour
10	Aspirin/NSAID hypersensitivity

^aSee Fig. 1.

- (3) Aspirin/NSAID hypersensitivity (see below).
- (4) Ingestion of pancakes or other meals containing wheat, corn, or oat flour.
- (5) Ingestion of more than 1 mg of mite allergen or more than 500 mites per gram of flour [9].

WHICH FOODS ARE THE TRIGGERS OF ORAL MITE ANAPHYLAXIS ?

Foods prepared with wheat flour, and more frequently pancakes, are the most common inducers of OMA. Hot cakes, beignets, pizza dough, sponge

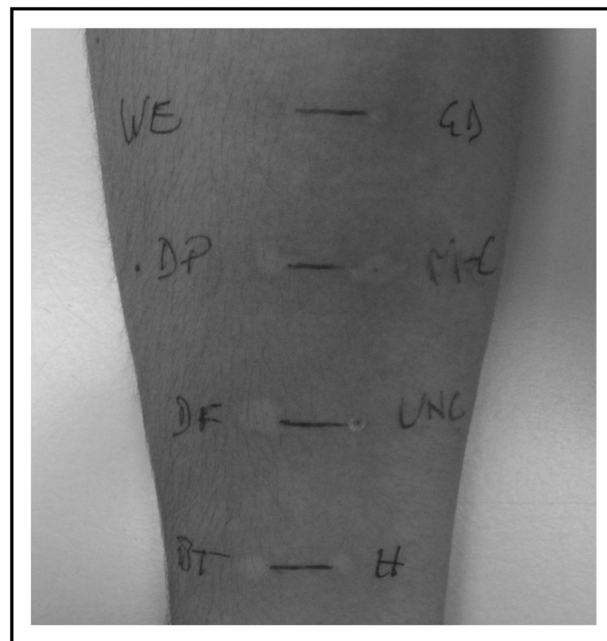


FIGURE 1. Immediate-type prick skin tests done to a patient with oral mite anaphylaxis. BT, *Blomia tropicalis*; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; GD, *Glycyphagus domesticus*; H, histamine; M-C, mite-contaminated wheat flour; UNC, uncontaminated wheat flour; WE, wheat commercial allergen extract.

cakes, cupcakes, Japanese pancakes (Okonomi-yaki, Tako-yaki), tempura, scones, steak or chicken parmigiana, and white sauce have also been involved. Foods made with corn flour (polenta, grits, corn cakes) may also be associated with OMA.

Storage time and condition of the flour are critical factors for mite contamination as flour stored at room temperature for longer periods of time are more likely to induce OMA [8]. The macroscopic aspect of the flour may be misleading as mite-contaminated flour may be indistinguishable from uncontaminated flour (Fig. 2).

Suesirisawad *et al.* inoculated six commercial brands of cooking wheat flour with *Dermatophagoides farinae* mites and stored them in four different containers at room temperature or at 4°C in a refrigerator. Levels of Der f 1 allergen increased at 6 weeks after inoculation and reached the highest levels at week 8. Samples stored at room temperature showed higher levels of mite growth, and no statistical differences were found among different types

of containers. In this study, wheat flour samples containing baking powder showed higher mite proliferation, and authors postulated that baking powder might change the texture of the flour, increasing aeration and facilitating mite proliferation [10].

WHAT ARE THE MITE SPECIES THAT HAVE BEEN ASSOCIATED WITH ORAL MITE ANAPHYLAXIS?

Both, domestic mites (*Dermatophagoides pteronyssinus*, *D. farinae*, *Blomia tropicalis*) and storage mites (*Tyrophagus* spp., *Aleuroglyphus ovatus*, *Tyrophagus putrescentiae*, *Suidasia pontifica*, *Tyrophagus entomophagus*, and *Blomia freemani*) have been identified in foods associated with the induction of OMA symptoms.

As clinical manifestations are triggered by cooked foods, it has been proposed that thermostable mite allergens might be involved in the pathogenesis of OMA [11]. Supporting this hypothesis, it

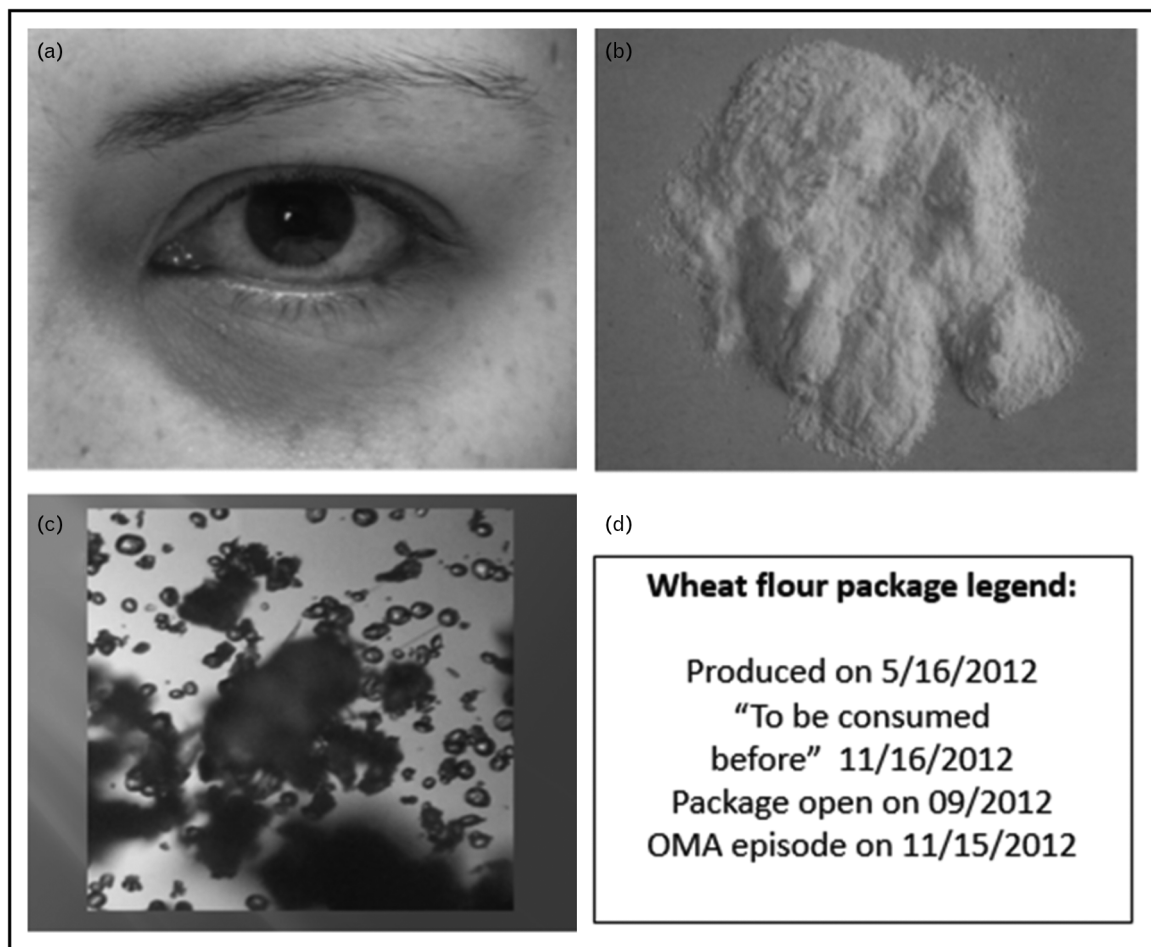


FIGURE 2. A 21-year-old female patient who developed oral mite anaphylaxis after eating pancakes. (a) Observe conjunctival injection and eyelid angioedema that began 20 min after eating. (b) The flour used by the patient for the preparation of pancakes. (c) Live *Dermatophagoides farinae* mites in the flour. (d) Information from the flour package legend.

has been demonstrated that heat-stable and digestion-stable food allergens, as exemplified by Ara h 2 from peanut, are more likely to produce severe reactions while heat-labile and digestion-labile molecules (e.g. Ara h 8) produce weaker or local reactions or are tolerated [12].

WHY STORAGE MITES CONTAINED IN THE FOOD CAN INDUCE ORAL MITE ANAPHYLAXIS?

Another interesting question concerning OMA would be why patients previously sensitized to domestic mites develop OMA when exposed to storage mites via the oral route. It is known that Pyroglyphid mites are highly cross-reactive, although they show limited cross-reactivity with *B. tropicalis* or with other storage mites from the Acaridae and Glycyphagidae families [13–15].

It is proposed that allergenic cross-reactivity between different domestic and storage mites could explain why patients sensitized to house dust mites may present systemic reactions when exposed to storage mites through the oral route.

WHAT ARE THE PATHOGENIC MECHANISMS INVOLVED IN ORAL MITE ANAPHYLAXIS?

The pathogenesis of OMA has not been completely elucidated. The most likely mechanism resides in the rapid absorption of mite allergens through the oral mucosa in a previously sensitized individual, resulting in mast cell/basophil activation from the interaction of allergen, specific IgE and high-affinity IgE receptors (FcεRI), with rapid mediator release and immediate onset of symptoms.

Additionally, other inflammatory pathways contributing to the pathophysiology and clinical severity of OMA could be activated by mite components. Among those, the following can be postulated: enzymatic action of mite proteases, which would disrupt mucosal tight junctions and enhance allergen penetration into the mucosal tissues [16]; stimulation of innate immunity, with activation of antigen-presenting cells and increased cytokine production [17]; dectin-2-glycan interactions [18]; and cyclooxygenase modulation with increased cysteinyl leukotriene production [19].

ORAL MITE ANAPHYLAXIS COMORBIDITIES AND RECENT FINDINGS

This section highlights some additional and new findings associated to OMA. They include the increased prevalence of NSAID hypersensitivity in

patients with OMA, exercise-induced anaphylaxis associated to OMA, OMA-simulating acute asthma, the occurrence of OMA in children, deaths attributed to OMA, OMA induced by contamination of oat flour with mites, and the simultaneous occurrence of OMA in more than one family member.

Aspirin/NSAID hypersensitivity

An increased incidence of aspirin (ASA)/NSAID hypersensitivity, more often manifested as angioedema, has been noticed in patients with OMA, as observed in a recent article in which 75 out of 170 cases of OMA (44.1%) had ASA/NSAID hypersensitivity [9]. The association of aspirin sensitivity, allergic rhinitis, and severe allergic reactions to ingested mites led us to propose ‘A New Aspirin Triad’ [20]. Currently, there is no clear understanding on the mechanisms responsible of this comorbidity, and various hypothetical pathways have been proposed [19].

Exercise-induced anaphylaxis associated to oral mite anaphylaxis

An association of OMA occurring during exercise after eating mite-contaminated foods, and mimicking wheat-dependent exercise-induced anaphylaxis has been reported in two patients, one in Caracas, Venezuela, and the other one in Japan [21,22]. A similar case was reported by Fiocchi *et al.* [23] who observed a 14-year-old asthmatic boy who suffered recurrent exercise-induced anaphylaxis after eating salami contaminated with the fungus *Penicillium lanoso-caeruleum* and running in the school or playing soccer.

Oral mite anaphylaxis mimicking acute asthma

A 10-year-old male patient developed breathlessness after eating a birthday sponge cake prepared with wheat flour contaminated with *A. ovatus* mite. Although he had mild allergic rhinitis, he had no previous history of asthma and was admitted to the hospital with the diagnosis of an asthma attack. From the analysis of this case, it was concluded that OMA can be misdiagnosed as asthma in the emergency room. It was also interesting to notice that the exposure to mite allergens through the oral route can induce acute bronchospasm in the absence of other symptoms (including angioedema), and gives further support to the concept of allergy as a systemic disease [24].

Oral mite anaphylaxis in children

Most cases of OMA have been diagnosed in young adults of any sex, with a mean age of 41 years.

However, OMA can be also observed in young children, as demonstrated in various reports from Japan, Taiwan, and Venezuela [25,26]. Some of these children who developed OMA had concomitant NSAID intolerance [7,27].

Death from oral mite anaphylaxis

There are in the literature a few fatality cases that were attributed to OMA. The oldest, published in 1963, was observed in a female patient who died after a massive ingestion of mites contained in a pap made with milk and wheat flour. Histopathologic examination demonstrated the presence of disseminated granulomas in multiple organs and numerous *Acarus siro* mites in stools and gut [28].

As already mentioned, OMA may present as a severe generalized reaction that may be life-threatening [29]. Most cases (>75%) are severe, grades III–IV [8]. More recently, additional deaths related to OMA have been reported [30–32].

Other foods that can induce oral mite anaphylaxis

Up to recently, most patients who developed OMA had been exposed to foods prepared with wheat flour. More rarely, corn flour used to prepare polenta, grits, and corn cake, was incriminated [2,33,34].

Miranda *et al.* recently reported a novel source of oral exposure to mites and induction of OMA, in which oat flour was involved in a 39-year-old female patient who experienced acute symptoms 1 h after taking a breakfast consisting of oat and milk. The microscopic analysis of the oat flakes evidenced the presence of abundant *S. pontifica* mites in the oat flour package [35].

Simultaneous occurrence of oral mite anaphylaxis in various family members

In general, more commonly OMA arises exclusively in one of the individuals who ingest the mite-contaminated food. This would suggest an individual predisposition to develop reactions to ingested mite allergens. There are, however, two recent reports in which OMA was observed simultaneously in more than one individuals exposed to the same food source.

Mangodt *et al.* observed an 18-year-old girl and her 48-year-old father who presented OMA 15–30 min after the ingestion of homemade apple beignets, whereas the mother and another daughter ate the same apple beignets without showing any untoward reaction [36].

Table 2. Prophylaxis of oral mite anaphylaxis

1	Reduced shelf life of packaged flour
2	Storing the flour in the refrigerator for 8 weeks or less
3	Store the flour in sealed glass containers or plastic bottles
4	Improved air quality, including air purifiers
5	Decrease intradomiciliary humidity
6	Cleaning and disinfection of furniture and floors
7	Use of acaricides

An additional report of simultaneous OMA in two sisters who ate pancakes at the same time has been very recently presented by Latour Staffeld *et al.* [37] in Santo Domingo, Dominican Republic. The study of the pancake mix demonstrated the presence of *Suidasia* spp. mites.

PREVENTION OF ORAL MITE ANAPHYLAXIS

As the macroscopic aspect of mite-contaminated flour may not be different from uncontaminated flour, it is difficult to predict the occurrence of OMA in an atopic at-risk patient. Furthermore, usually flour packages are left open at room temperature in the pantry, in locations with temperature and humidity conditions favoring mite proliferation (temperature higher than 27 °C, and relative humidity higher than 70%).

The implementation of preventive measures for OMA is further complicated when eating outside from home, as in restaurants and other public places. In general, the main preventive recommendation is to avoid eating foods prepared with flour stored at room temperature for more than 8 weeks [10]. Table 2 presents the strategies currently recommended to prevent OMA [10,38].

CONCLUSION

OMA is an acute, potentially lethal, allergic disorder occurring immediately after the ingestion of mite-contaminated foods. Physician awareness on this clinical entity is required to adequately suspect, diagnose, treat, and prevent its manifestation through simple measures recommended to be implemented by patients and family members at risk.

Among unmet needs that require additional research on OMA, a better knowledge of its pathogenetic pathways, the role of oral exposure to mite allergens in the food on the induction of sensitization or tolerance (especially at early ages), and more efficient methods of prevention and treatment, including immunotherapeutic approaches, are to

be pursued. OMA may be an underdiagnosed medical problem, and more effort should be made to clearly define its worldwide distribution and incidence.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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This article shows that OMA can also occur in countries with temperate climate.

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