



Hidden allergens and oral mite anaphylaxis: the pancake syndrome revisited

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Purpose of review

To present currently available information on oral mite anaphylaxis.

Recent findings

Oral mite anaphylaxis (pancake syndrome) is a new syndrome characterized by severe symptoms triggered by the intake of foods containing mites and their allergens. Breathlessness, face and/or laryngeal angioedema, wheezing, rhinorrhea, cough, dysphagia, and wheals are the most frequent clinical manifestations.

Summary

Pancake syndrome can occur in individuals at any age and in any geographical location. Foods made with wheat and corn flour, especially pancakes, are the most common inducers of the clinical picture. Both, domestic and storage mites have been incriminated. Increased physician awareness is required for early diagnosis and treatment, and for the prevention of future episodes in predisposed individuals.

Keywords

anaphylaxis, *Dermatophagoides* spp., mites, pancake syndrome, storage mites

INTRODUCTION

Oral mite anaphylaxis (OMA), also called pancake syndrome, is a newly recognized clinical syndrome characterized by severe, potentially life-threatening, allergic symptoms occurring in allergic individuals after exposure through the oral route to foods containing mites. First described in 1993 [1], this syndrome is being observed with increasing frequency in different areas of the world and has been considered as an experiment of nature where the contact with mite allergens occurs at the oral and gastrointestinal mucosal level instead of through the respiratory mucosa as observed in asthma and rhinitis.

This article reviews the information currently available on OMA, indicating some unexplored areas needing further research to ascertain more clearly its mechanisms. These findings may provide additional clues about the pathogenesis of allergic diseases, particularly anaphylaxis.

HIDDEN FOOD ALLERGENS

Various food contaminants are capable of inducing allergic and pseudoallergic reactions. These contaminants may be present in different types of food. Microorganisms such as bacteria, molds, viruses, and parasites, toxins, chemical substances, food

additives (dyes, preservatives), food allergens, cross-reacting allergens from pollens, other foods and latex, and drugs may be present [2].

Domestic mites are one of the most important allergenic sources involved in allergic diseases such as rhinitis, asthma, and atopic dermatitis. Mucosal tissues of the respiratory tract, conjunctiva, and the skin are the main sites of contact with mite allergens. Since the first descriptions of allergic reactions to mites contained in the food, it has now been widely recognized that mites should be regarded as an additional source of hidden food allergens.

ORAL MITE ANAPHYLAXIS

The first report of anaphylaxis induced by the ingestion of food contaminated with mites was published

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KEY POINTS

- OMA (pancake syndrome) is a new disease characterized by severe symptoms triggered by the intake of foods containing mites and mite allergens.
- It has been observed in individuals of any age and in different areas worldwide.
- Foods made with wheat and corn flour, especially pancakes, are the most common inducers of this clinical picture.
- Both domestic and storage mites have been incriminated.
- Physician awareness is crucial for early diagnosis and treatment, and for the prevention of future episodes in predisposed patients.

by Erben *et al.* [1]. Mites have long been recognized as contaminants of foods such as flour, cheese, ham, chorizo, salami, grain, cereals, dried fruits and vegetables, pet foods, tealeaves, dried milk, and sugar (Fig. 1) [3].

It has also been shown that mites may be present in paper, tobacco, molds, bird, and animal nests [4]. In fact, mites are inoculated in some cheeses previous to the ageing process to develop particular characteristics such as a nutty and fruity flavors and aroma and a distinctive appearance [5]. A 'Cheese mite dermatitis' was observed in 1948 by Anderson and Fishman [6]. 'Cheese itch', a contact dermatitis due to mite-infested cheese dust, was reported by Dowling and Prosser Thomas in 1942 [7].

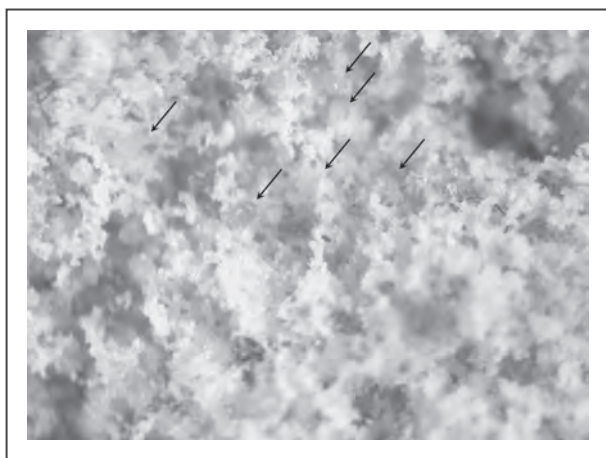


FIGURE 1. *Dermatophagoides pteronyssinus* growing on wheat flour and baker's yeast in the laboratory at humidity and temperature conditions mimicking those of the home environment. The arrows point at different mites. Picture taken by Eva A. Fernández at Inmunotek.

OMA (pancake syndrome or pancake anaphylaxis) can be defined as the occurrence of severe allergic symptoms beginning immediately after eating foods contaminated with mites, more often wheat flour. After the original report, new cases have been reported from various regions of the world [8^{***}].

CAUSE

Foods prepared with mite-contaminated wheat flour have been most frequently implicated as the cause of OMA. Foods such as pancakes, beignets, pizza dough, Japanese pancakes (okonomi-yaki, takoyaki) [9[¶]], scones, sponge cakes, grits, white sauce, tempura batter [10[¶]], and grated bread used to prepare parmigiana steak have been frequently incriminated. Corn flour utilized in the confection of polenta and corn cakes has also been involved, although less frequently.

Older foodstuffs are more prone to induce OMA than fresh flour. Under optimal conditions for mite growth, longer storage times have been associated with increased frequency of OMA [9[¶]], which indicates that an increasing concentration of allergen is a further risk. Therefore, the time for consumption of the stored flour is important, particularly when stored on the kitchen shelf after being opened. The macroscopic aspect of the flour is misleading, as although older contaminated flour may appear damp and yellow colored, flour with 'normal' aspect (white, dry) may also contain large amounts of mites. Light microscopy is needed to firmly establish the presence of mites (see Fig. 1). We screened 35 unselected flour samples in Caracas and mites of five species (*Suidasia* spp., *Dermatophagoides pteronyssinus*, *Aleuroglyphus ovatus*, *Lepidoglyphus destructor*, and *Blomia tropicalis*) were present in 13 samples (37.1%) [11].

Domestic and storage mites have been implicated among the mite species inducing OMA, including *D. pteronyssinus* and *D. farinae*, *B. tropicalis* and *B. freemani*, *Suidasia medanensis*, *A. ovatus*, *L. destructor*, *Tyrophagus putrescentiae*, and *Tyrophagus entomophagus*. Most patients who have experienced OMA have been generally sensitized to domestic and storage mites. Therefore, we hypothesized that this fact might be related to extensive cross-reactions between allergens from different species of mites [12,13^{***}]. Only some allergic patients who are exposed to mite-contaminated flour develop OMA. However, since there are other clinical associations (e.g. NSAID hypersensitivity), it is likely that there are other unknown predisposing factors such as a genetic condition.

It is becoming increasingly evident that most mite species contain the majority of the allergens

described so far, although differences may occur in the primary structure of the allergenic molecules. From the 24 currently described mite allergens, 13 are present in at least five species. We further speculate that the allergen, or allergens, involved in these reactions should be heat stable, such as group 2 mite allergens, to withstand the heating process to which the flour is subjected.

Although OMA could be triggered by cheese, salami, ham, chorizo, tealeaves, and other foods contaminated with mites, there are fewer reports related to the induction of OMA by other foodstuffs in the literature.

A great deal of attention has been given in the lay press and social media, especially in North America, to the possible human health effects of cheese mites present in large quantities in cheeses produced in France (Mimolette) and Germany (Milbenkäse, literally mite cheese). However, the medical implications of such exposures are presently unknown, since no cases of OMA due to those cheeses have been reported, and no specific regulations have been proposed by the regulatory authorities.

Melnyk *et al.* [5] observed that *Acarus siro* was the mite present in Mimolette, and *Tyrophagus casei* in Milbenkäse cheese. Other mite species present in cheese identified in the United States of America are *Neocotyledon rhizoglyphoides*, *A. immobilis*, *T. casei*, *A. farris*, *A. chaetoxysilos*, *Tyrophagus longior*, *T. putrescentiae*, *T. nelswanderi*, and *T. palmarum*.

Occupational diseases caused by mites, especially in the grain industry workers, have been reported in the medical literature. The main reported symptoms were respiratory (asthma), and cutaneous (contact dermatitis) [14].

PREVALENCE

The prevalence in the general population is currently unknown, since only isolated case reports and small series of patients with OMA have been published. However, in certain areas it might be more prevalent than reported, since most cases are not recognized and may be classified as 'idiopathic' anaphylaxis. In one study performed in our institution, OMA was the third cause of anaphylaxis (7.2%) only after drugs and foods. This rate may be slightly influenced by a higher recognition and awareness by local physicians and the experience of our group in dealing with this medical entity [15].

Series of patients with OMA have been reported from Caracas (Venezuela), Canary Islands (Spain), and Japan [9,11,16–17]. All cases reported from Spain were observed in the Canary Islands, which are characterized by a subtropical climate. Other

Table 1. Oral mite anaphylaxis: demographics

Number of cases	145
Age range	8–71 years
Sex: female/male	86/59
Location	Spain 59 Japan 40 Venezuela 33 USA 7 Brazil 2 Singapore 2 Taiwan 1 Panama 1
Foods	Pancakes, beignets, pizza dough, okonomi-yaki, tako-yaki, tempura, polenta, scones, grits
NSAID hypersensitivity	61/145 (42.0%)

cases were observed in the United States, Brazil, Taiwan, Singapore, and Panama (Table 1). We are aware of unpublished cases from Dominican Republic, Israel, Peru, Colombia, New Zealand, Mexico, and Thailand. Up to now, 145 cases of OMA have been reported, but, as mentioned earlier, many cases may not be recognized and reported.

OMA is observed more frequently in geographical locations with high temperatures (>27°C) and relative humidities (>70%), which favor mite proliferation. These characteristics are highly prevalent in tropical and subtropical areas of the world. The episodes of OMA may occur in locations, which are distant from the place where the flour was purchased. Examples are a beignet mix produced in New Orleans, Louisiana, and shipped by mail to the northern United States (of Minnesota and Michigan), pancakes made with wheat flour purchased in New York causing OMA in Caracas, Venezuela, or beignet flour purchased in New Orleans and eaten in Santo Domingo, Dominican Republic. In conclusion, OMA can be observed in areas different from the tropics. In these cases, it was not clear where the flours were contaminated. It raises the possibilities that the flour samples were contaminated either in the place of origin or after storage at destination.

In any case, flour should be stored in a refrigerator in a sealed container or consumed after opening the container for the first time, especially in tropical and subtropical regions. The presence of storage mites in flour samples may be conditioned by the more prevalent presence of storage mites in the kitchen and food storage cabinets.

In conclusion, OMA can occur in areas different from tropical and subtropical areas, independently

from where the flour was purchased, and flour should be kept in sealed containers in a refrigerator, once opened.

CLINICAL ASPECTS

As previously mentioned, 145 cases of OMA have been published up to now worldwide. Patients of any age and social condition have been reported, with an age range between 8 and 75 years, and an increased frequency in females. Symptoms begin rapidly after food intake, generally within 10–45 min. All patients have an atopic background, with a previous history of allergic rhinitis, asthma, or both, and show positive prick skin tests to mite allergenic extracts.

Most common symptoms are breathlessness, face and/or laryngeal angioedema, wheezing, rhinorrhea, cough, dysphagia, and wheals. Less frequently abdominal cramps, conjunctival erythema and itching, sneezing, vomiting, and tachycardia are present. According to the clinical severity scores, most cases, up to 75%, are severe [9[¶]]. Acute respiratory failure with cyanosis can occur and requires transfer of the patient to the ICU for intubation and respiratory assistance. There are two reports of death related to OMA in the literature [18,19].

The association of OMA with exercise-induced anaphylaxis has been reported by two groups of

investigators, and this clinical pattern has been designated as dust mite ingestion-associated exercise-induced anaphylaxis [20,21].

Out of the 145 reported cases of OMA 61 (42.0%) show cutaneous aspirin/NSAID hypersensitivity (acute urticaria and/or angioedema in the absence of chronic spontaneous urticaria). This association has no clear explanation and various possibilities have been put forward, including the modulation of cyclooxygenase-1 activity by mite constituents (see below, section on pathogenesis) [22[¶]].

PATHOGENESIS

Mites that have been associated with the production of OMA belong to the families Pyroglyphidae (*D. pteronyssinus* and *D. farinae*), Glycyphagidae (*L. destructor*), Echimyopodidae (*B. tropicalis* and *B. freemani*), Acaridae (*A. ovatus*, *T. putrescentiae*, *T. entomophagus*), and Suidasiidae (*S. medanensis*) (Table 2).

Oral provocation with mite-contaminated flour performed by Blanco *et al.* reproduced the clinical picture in three patients [16]. Additionally, some patients experience recurrent episodes of OMA triggered by food prepared with the same contaminated flour before the source of symptoms is identified and avoided.

As symptoms of OMA appear when heated foods are consumed, it was suspected that heat resistant

Table 2. Mites responsible for oral mite anaphylaxis according to the geographical location

Country	City	Mites
Brazil	Porto Alegre	<i>Tyrophagus</i> spp. <i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i>
Brazil	Rio de Janeiro	<i>Aleuroglyphus ovatus</i>
Japan	Kumamoto	<i>Tyrophagus putrescentiae</i>
Japan	Kanagawa	<i>Tyrophagus putrescentiae</i> <i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i>
Panama	Panama City	<i>Blomia tropicalis</i> <i>Dermatophagoides pteronyssinus</i>
Singapore	Singapore	<i>Dermatophagoides farinae</i>
Spain	Canary Islands	<i>Dermatophagoides farinae</i> <i>Tyrophagus entomophagus</i>
Taiwan	Taipei	<i>Blomia freemani</i>
United States	Detroit, Philadelphia, Birmingham, New Orleans, Minnesota, Danbury, Charlottesville	<i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i>
Venezuela	Caracas	<i>Dermatophagoides farinae</i> <i>Suidasia</i> spp. <i>Aleuroglyphus ovatus</i>

mite allergens were responsible for the clinical picture. This hypothesis was confirmed by means of skin testing mite-sensitive volunteer individuals with unheated and heated mite-contaminated wheat flour. The diameters of skin tests were significantly reduced by heating of the flour, but skin tests were still positive, with a mean wheal diameter of 7 mm. These results suggested that group 2 mite allergens (which are termoresistant) were involved while group 1 allergens (termolabile) were denatured by heating. In fact, group 2 but not group 1 allergens are predominant in the contaminated flours [8²², 10²⁴, 23–25]. As a related observation it is interesting to mention that termoresistant food allergens are known to induce more severe reactions than the termolabile ones.

The allergenicity of mites has been demonstrated in many ways. Mites produce potent allergens that bind specific IgE *in vivo* and *in vitro*, induce positive immediate-type skin tests, and trigger allergic symptoms after challenge through nasal, ocular, or inhalation routes. Also, allergen-specific immunotherapy with mite allergens given by the subcutaneous or mucosal routes is effective and commonly used for the treatment of allergic respiratory diseases.

Other than IgE-mediated hypersensitivity, alternative mechanisms may be operative for the induction of symptoms when mites and their allergens are ingested in the food. First, allergen proteases disrupt the tight junctions of epithelial surfaces on the mucosal tissues [26,27]. Second, Der p 2, the main allergen from *D. pteronyssinus*, has structural and functional homology with myeloid differentiation factor 2, the lipopolysaccharide-binding component of the TLR4 signaling complex of innate immunity. The interaction with TLR4 through this molecular mimicry is able to trigger the activation of antigen-presenting cells, cytokine production, and inflammation [28]. Third, mite allergens can induce epigenetic changes [29]. Fourth, mites can produce substances that inhibit cyclooxygenase-1 (COX-1) [30].

More than 40% of patients who develop OMA show hypersensitivity to aspirin and other COX-1 inhibitors, which is manifested as acute urticaria and/or angioedema, the 'New Aspirin Triad' [31]. The reasons for this association have not been clarified, although an increased prevalence of aspirin hypersensitivity has been previously observed in atopic mite-sensitive individuals [32]. On the other hand, we have observed that mite allergenic extracts inhibit COX-1 *in vitro* [30]. Another relevant observation is that *Dermatophagoides* extracts stimulate the production of cysteinyl

leukotrienes by bone marrow-derived dendritic cells and enhance the generation of leukotrienes by bone marrow mast cells transfected with dectin-2. It was proposed that this stimulatory activity is related to a glycan-dectin-2 interaction [33].

RISK FACTORS AND DIAGNOSIS

Although it is not clear why only a subset of mite-allergic patients develops OMA, some predisposing conditions have been identified. They include a history of atopic respiratory disease (rhinitis, asthma), sensitization to mites, cutaneous ASA/NSAID hypersensitivity, and the ingestion of foods containing mites.

For the diagnosis of OMA the following criteria should be taken into consideration:

- (1) Compatible symptoms after eating foods made with flour (wheat, corn).
- (2) Previous history of allergic rhinitis and/or asthma.
- (3) In-vivo or in-vitro demonstration of sensitization to mites.
- (4) Positive skin tests to extracts of the incriminated flour (Fig. 2).
- (5) Negative skin tests to wheat allergenic extract and uncontaminated flour.
- (6) Clinical tolerance to foods made with uncontaminated flour.
- (7) Microscopic identification of mites in the flour (Fig. 3).
- (8) Presence of mite allergens in the flour.

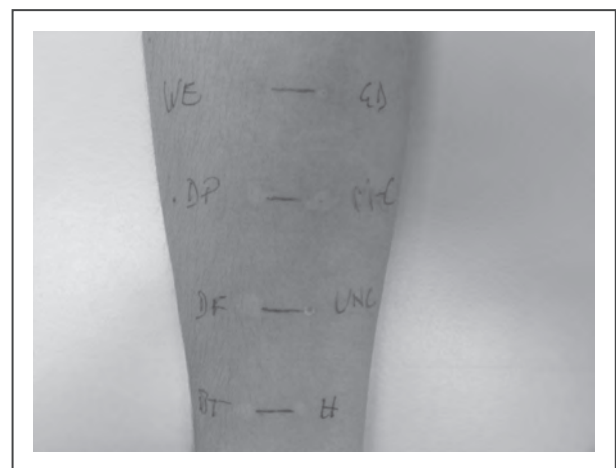


FIGURE 2. Skin prick tests in a patient with oral mite anaphylaxis. Wheal diameters (in mm): glycerosaline solution 0, wheat allergenic extract 2, *D. pteronyssinus* 11, *D. farinae* 10, *L. destructor* 3, *G. domesticus* 4, mite-contaminated flour 14, uncontaminated flour 2, and histamine 7.

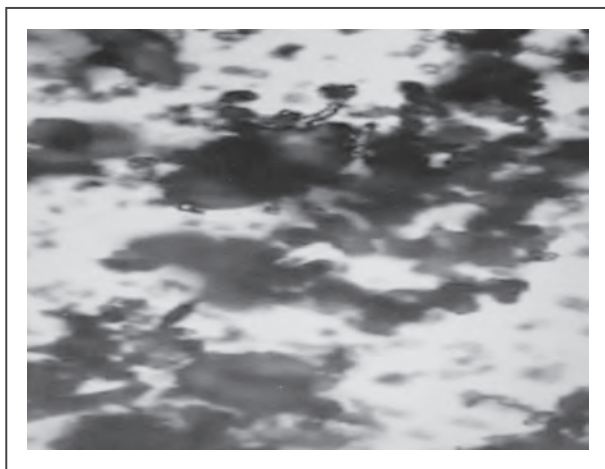


FIGURE 3. Wheat flour contaminated with mites (10× magnification).

PREVENTION

Prophylactic measures that can be implemented for patients at risk for OMA include:

- (1) Reduced shelf life of packaged flour in the grocery store.
- (2) Store the flour in the refrigerator for less than 6 weeks [34].
- (3) Store the flour in sealed glass containers or plastic bottles.
- (4) Improved air quality using air purifiers.
- (5) Decrease of intradomiciliary humidity.
- (6) Cleaning and disinfection of furniture and floors.
- (7) Use of acaricides and reduction of allergen exposure throughout the house.
- (8) Improve cleaning in the kitchen, pantry, and cabinets.

CONCLUSION

OMA is a severe, life-threatening condition that in many cases is underrecognized and undertreated. Physicians should suspect it when confronted with patients who present severe allergic symptoms temporally associated to the ingestion of meals containing flour. Increased awareness and the implementation of preventive measures may be effective to reduce morbidity and fatalities from this disease.

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Conflicts of interest

There are no conflicts of interest.

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