



Dust mites living in human lungs – the cause of asthma?

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Received 3 December 2003; accepted 11 February 2004

Summary Asthma does not have a clear cause and may represent a cluster of diseases. We propose that asthma in house dust mite sensitive patients may be caused by recurrent inhalation of live dust mites which are able to live for some time in the bronchioles of the lung. To provide themselves with a food source, the mites may purposefully excrete proteolytic enzymes, including Der p1, which increase epithelial shedding by freeing cells from the basement membrane. The mites then feed on the shed respiratory epithelial cells. Consequent loss of an intact respiratory epithelium exposes underlying tissues to dust mite protein and other allergens triggering sensitisation to these proteins. Later, repeated infestation provokes an allergic response which manifests itself as asthma attacks.

The evidence for this hypothesis was tested against the Bradford–Hill criteria for causation; consistency, strength, temporal association and dose response. Potential areas for further research were also identified. The association between asthmatic symptoms and pulmonary acariasis was consistent across a number of studies. Determining the strength of the association and any dose response requires more work which is dependent on the development of better tests for the detection of mites in sputum. There was tentative evidence of a temporal association in the published studies identified. Biological plausibility and experimental evidence was available for pulmonary acariasis in primates and arsenic treatment was effective in humans.

Better tests for mites in sputum are needed, as is work to assess more modern anti-acaricidal drugs in dust mite sensitive asthmatics.

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Introduction

Asthma is “a chronic inflammatory disease of the bronchial airways, which is characterised by a desquamative eosinophilic bronchitis”. The defining clinical characteristics of asthma is “reversible airway narrowing and increased airway responsiveness to non-specific provocative stimuli” [1].

Consequently, asthma may represent a cluster of diseases with a common symptomatology.

Dust mite allergy is common in asthma. Around 65% of asthmatics have an allergy to house dust mites [2] and over 90% of dust mite allergic individuals have IgE to Der p1 [3]. There is some evidence that initial exposure to house dust mite allergens and in particular Der p1, can trigger sensitization to the allergen. In other words, that Der p1 may be causally linked to the origin of asthma in some individuals [3]. Repeated exposure

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to Der p1 can then trigger an allergic response in sensitised individuals.

What is Der p1?

House dust mites are known to produce a range of potent allergens called Der p and Der f antigens after the two commonest house dust mites, *Dermatophagoides pteronyssinis* and *Dermatophagoides farinae*. These antigens are proteolytic enzymes. Der p1, which has been extensively studied, is produced in the mid gut of the house dust mite where it aids in the digestion of proteins including human keratin which is an important food source for dust mites [4]. In the lungs, Der p1 can directly digest the respiratory epithelium increasing the permeability of the epithelium and increasing the movement of allergens into the tissues where a number of inflammatory pathways are affected [3].

The hypotheses

Our hypothesis is that asthma in house dust mite sensitive patients may be caused by recurrent inhalation of live dust mites which are able to live for some time in the bronchioles of the lung and that. To provide themselves with a food source, the mites excrete proteolytic enzymes, including Der p1, which increase epithelial shedding by freeing cells from the basement membrane. The mites then feed on the shed respiratory epithelial cells. Consequent loss of an intact respiratory epithelium exposes underlying tissues to dust mite proteins and other allergens triggering sensitisation to these proteins. Later, repeated infestation provokes an allergic response which manifests itself as asthma attacks.

The evidence

The evidence for this hypothesis may be considered under a revised version of Bradford and Hills criteria for causality; consistency, strength, temporal association, dose response, plausibility and experimental evidence [5].

Consistency

Pulmonary acariasis, that is the presence of mites in the lungs, is well recognised in primates and has been described in a range of birds, insects and

other animals [6]. However, a wide range of mites have been described in human sputum samples including: *Acarus siro*, *Aleuroglyphus ovatus*, *Tyrophagus putrescentiae*, *Caloglyphus berlesei*, *C. myoophagus*, *Cheyletus eruditus*, *D. farinae*, *D. pteronyssinus*, *Euroglyphus maynei* and *Tarsonemus granarius*. Many of these are storage or dust mites. Studies which have shown mites in sputum samples are shown in Table 1.

The first description of mites in sputum was in 1944 [7] when mites were found in the sputum of 17 out of 28 asthmatics admitted to a local hospital in Ceylon. The authors were initially concerned that the samples had become contaminated as they could readily identify the same mites in ward and laboratory dust and air samples. However, stringent precautions to exclude contamination did not change the findings.

In at least one case with chronic severe 'asthma', the authors were convinced that mite infection in the lungs had been present for at least seven months. Cases often had a blood eosinophilia and usually did not have a family history of asthma. The cases responded to treatment with arsenic. Increased numbers of mites were seen in the sputum in the first few days after treatment (particularly after the first dose) and many of the mites which were seen were in a macerated condition suggesting the mites had been killed by the arsenic treatment. Symptoms usually subsided over the following two months.

Subsequently, Soysa and Jayawardena [8] published a paper accompanied by a BMJ editorial [9] describing a cases series of 30 Ceylonese soldiers with 'eosinophilic bronchitis' of whom 11 had shown mites in the sputum. Most of the individuals were regularly exposed to dust from cereals, pulses, flour, sugar, tea, coffee and other dried army rations or to dust in linen or leather stores. They had complained of 'asthma' for between 3 weeks and 18 years. Once again, the cases responded to arsenic although spontaneous remission occurred in some cases.

Two years later Wilson [10] identified mites in the sputum in three of 28 cases of "tropical eosinophilia" in East Africa. As in the two studies above, an Herxheimer type reaction was noted on day 2–5 of treatment suggesting that killing the mites in the lungs had released a flood of antigens causing a temporary exacerbation of symptoms. In all three cases mites and ova were only discovered in the sputum after the initiation of arsenic treatment. This suggests that when alive the mites cling tenaciously to the walls of the airways but once dead lose hold and are more easily expectorated [11].

Table 1 Studies demonstrating mites in sputum samples

Author and location	Findings
Carter et al. [7], Ceylon	Mites in 17 of 28 asthmatic patients. Marked blood eosinophilia in most cases
Soysa and Jayawardena [8], Ceylon	Mites in sputum of 11 of 21 cases where sputum was available in a case series of 30 patients with 'eosinophilic bronchitis'
Van der Sar [14], Curacao	Mites in 8 asthmatics, most with eosinophilia
Hall [13], England	1 case in a fruitier
Soysa [19], Celon	Mites seen in sputum samples of 42 of 67 cases where sputum was available in a case series of 100 cases with 'eosinophilic respiratory syndrome'
Wilson [10], East Africa	Mites in 3 of 28 cases of 'tropical eosinophilia'
de Figueroa Taboa [12], Spain	Details provided on one of several cases where mites were found in the sputum
Kijima [15], Japan	One patient where mites and eggs were found in the terminal bronchioles of a resected segment of lung
Farley et al. [16], Texas, USA	Mites in 55 respiratory specimens including spontaneous and aerosol induced sputum and a fine needle aspirate. Eggs were seen in 5 cases
	The highest prevalence 2.7% was in aerosol induced sputum samples
Chen et al. [17], China	Mites were found in the sputum of 92 of 363 employees in grain stores or in herbal medical stores. 65 of the 92 were symptomatic
Li and Li [18], China	Mites were found in the sputum of 49 of 924 employees in grain stores or in herbal medical stores. 22 of the 49 cases had eosinophilia

Further cases have been described in Spain [12], England [13] and the Curacao [14]. In another case in Japan [15], mites were identified initially in the sputum and later in the terminal bronchioles of a partially resected lung together with a number of eggs. In Texas, USA, 55 sputum samples examined over a 4.5 year period were found to contain mites, eggs or larval forms [16].

More recently Chinese research groups have undertaken two surveys of pulmonary acariasis in workers in grain and herb stores. In the first series 92 of 363 persons had mites in their sputum, of whom 65 had respiratory symptoms and blood eosinophilia [17]. In the second series 49 of 924 subjects had mites in their sputum, of whom 22 had an eosinophilia [18].

Strength

Soysa [19] found no mites in the sputum of 14 controls in good health but mites in the sputum of 42 of 67 cases of 'eosinophilic respiratory syndrome'. However, no assessment has been made regarding the strength of the association between the presence of mites and acute asthmatic attacks in asthmatics with desquamative eosinophilic bronchitis and house dust mite allergy.

Temporal association

Moving asthmatics to stay at an altitude at which dust mites may not be able to survive, reduces

asthmatic symptoms including sputum eosinophilia and the number of epithelial cells in sputum. Returning to a house at a lower altitude which contains house dust mites once again increases the shedding of epithelial cells and the level of sputum eosinophilia to levels similar to those which were present before removal from exposure to house dust mites [20]. However, the presence of mites in the lungs prior to the onset of asthma was not assessed in this study.

Asthma attacks only occur after initial sensitisation to an allergen [3]. Tentative evidence that the onset of sensitisation may be related to exposure is provided by a study which showed that the mean age of onset of sensitisation to house dust mites is 6.7 years but 18.7 years for storage mites [21].

Soysa and Jayawardena [8] retrospectively assessed the occupation of 11 cases with mites in the sputum and found that they had all worked in dusty environments. Soysa [19] also believed that eight patients had a recurrence of symptoms due to re-infection with mites after successful treatment when the patients returned to their previous occupation.

Dose response

A dose response has not been shown as the number of mites recovered in the above studies bore no relationship to symptoms. However, this criterion may not be directly applicable. There is evidence

in another mite disease, scabies, that a reaction to infestation does not become apparent until sensitisation occurs, which takes two months after first exposure and 1–4 weeks in subsequent exposures [11,22].

Plausibility

There is a parallel in another primate species. Up to 100% of Old World monkeys have pulmonary acariasis [23], although different mite species are involved. The inhalation of mites also appears plausible when examined in detail.

It is reasonable to presume that if a person's nose is pressed into a pillow mites will be inhaled from time to time. Mite density in mattresses can be around 20,000/m³ or 1 mite/5 cm³ [24]. In addition, the human lung is in contact with 15,000 l of air per day [25] or 5000 l during 8 h in bed at night. Brushing the surface of bedding or using a vacuuming appliance to suck on a pillow often demonstrates the presence of dust mites. The size of the mites means that most would be deposited in the upper airways or the trachea rather than in the bronchioles. However, they would probably be able to crawl deeper into the lungs [16].

Experimental evidence

Pulmonary acariasis in monkeys can very effectively be treated with ivermectin [6]. This has not been tried in humans. However, several of the studies mentioned above demonstrated that arsenic was effective in treating human pulmonary acariasis [8,10,11,19]. In vitro, arsenious oxide at a concentration of 1:1000 has been shown experimentally to kill *Tyroglyphus longior* in 10 min [11]. A Herxheimer type reaction was also noted 3–5 days after arsenic treatment in several of the studies and an increase in the number of dead or decayed mites were demonstrated in the sputum after treatment was instituted. This suggests a causal link between arsenic treatment and an effect from killing mites in the lungs.

Mebendazole has also been used in the treatment of asthmatics in a randomised controlled trial in Spain and was shown to be of some benefit [26]. The authors suggested that this might be due to an immunomodulatory effect of mebendazole. However, it is reasonable to suggest that mebendazole would be effective against mites and that the medication may have had a beneficial effect by killing mites present in the lungs.

Other considerations

Enzymatic effects of Der p1 on the airways have been shown to be important in the development of asthma as Der p1 can destroy adjacent areas of respiratory epithelium exposing the underlying tissues to Dep p1, precipitating an allergic response [3]. However, fresh Der p1 regurgitated or excreted by live house dust mites in the lungs is more likely to be enzymatically active than old Der p1 in the environment which is likely to have degraded and to have been coated with other dust particles.

Trials of the removal of dust mites from the environment of asthmatics have been largely unsuccessful, suggesting that a reduction in exposure to Der p1 in dust in the environment of asthmatic patients does not in itself reduce exposure to the cause of asthmatic symptoms [2].

Why this hypothesis has not been explored before

There are several possible reasons for this. Firstly, house dust mites were not discovered as the cause of house dust allergy until 1967 [27] by which time interest in mites in the lungs had been lost. Secondly, the identification of allergens, such as Der p1, has led to the assumption that the allergen is the problem, rather than the assumption that the allergen is a marker of infestation. Thirdly, the process for identifying mites is very slow, taking up to five days to scan the sputum slides of one patient. Fourthly, except in a few severe cases, only one mite was found in sputum even when examining 5–40 ml of sputum. Finally, many of the papers emphasise that mites are easily mistaken for food contaminants and are not easily identified by the untrained eye.

Problems with the hypothesis

The most significant problem with this hypothesis is that although dust mites including *Dermatophagoides* have been found in sputum, most of the mites found have been storage mites. This may be because *Dermatophagoides* were regarded as a rare mite when first identified as the allergen in house dust [27]. The entomologist involved in the first study [7] thought that the mites were *Tyroglyphus longius* [28] although there is the suggestion in the paper that there was some uncertainty in the

identification of the mites. He demonstrated that the same mites were ubiquitous in hospital dust samples and large numbers were found in a small piece of fluff taken from inside a spring wire mattress.

Further work

Further work is needed to test this hypothesis. A faster test for mites in sputum, for example a monoclonal antibody test for mite exoskeleton, with a known sensitivity and specificity is needed. The prevalence of mites in induced sputum samples in asthmatics with a raised levels of eosinophils and epithelial cells in sputum [20] also needs to be determined. Randomised controlled trials of anti-acaritic medication such as mebendazole and ivermectin could follow if mites were found.

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