



Characterization of a cohort of storage mite sensitized subjects

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Abstract

Purpose Storage mites (SM) are ubiquitously found close to human habitation and are a source of allergic reactions ranging from allergic rhinitis and asthma to anaphylactic reactions.

Methods Data on 3997 patients with suspected allergic rhinitis were included. We performed correlation of intradermal testing and specific IgE-test results using Cohen's kappa and univariate logistic regression to evaluate the probability of symptoms and the point of time symptoms were reported. In some patients nasal provocation was performed to prove allergic rhinitis.

Results Patients with storage mite sensitization show a high degree of cross reactivity between different storage mite species. Cross reactivity of storage mite species with house dust mites (HDM) was found in 56% and is only slightly higher than that of other common allergens such as grasses (45%) or birch (42%). A correlation of intradermal testing and specific IgE testing could not be found. The most common symptoms of sensitized subjects were nasal obstruction and hyposmia and symptoms were dependent on presence of chronic sinusitis. Nasal provocation was positive in 16 to 33% of subjects tested.

Conclusions SM are a common sensitization in the study population and should be included in standard skin prick test arrays. Cross sensitization to house dust mites is limited and nasal symptoms are most frequent. Nasal provocation testing is necessary to secure clinical diagnosis of allergy and further research is needed to evaluate the clinical relevance of the high sensitization rates found for intradermal testing.

Keywords Allergic rhinitis · Specific IgE · Intradermal testing · Skin prick test · Symptoms of allergy · House dust mites

Introduction

Storage mites (SM) are ubiquitously found close to human habitation in stored food especially grain or flour, in hay and straw, in livestock feed and food for domestic animals but also in in house dust [1–3]. SM belong to the Glycyphagidae family (*Blomia*, *Lepidoglyphus*, and *Glycyphagus* genera) and the Acaridae family (*Tyrophagus* and *Acarus* genera) (Fig. 1). Clinical relevant species include *Acarus siro*, *Tyrophagus putrescentiae*, *Lepidoglyphus destructor* and *Glycyphagus domesticus* [1, 4].

They produce allergens and may be a cause of rhinitis, asthma and other allergic reactions up to anaphylactic reactions also known as “pancake syndrome” [6]. Sensitization against storage mites is especially often found among farm workers, millers and bakers but cases of sensitization have also been reported in urban populations without occupational exposure [2, 3, 7–10]. Overall sensitization rates are given between 11.2 and 18.96% [11–14].

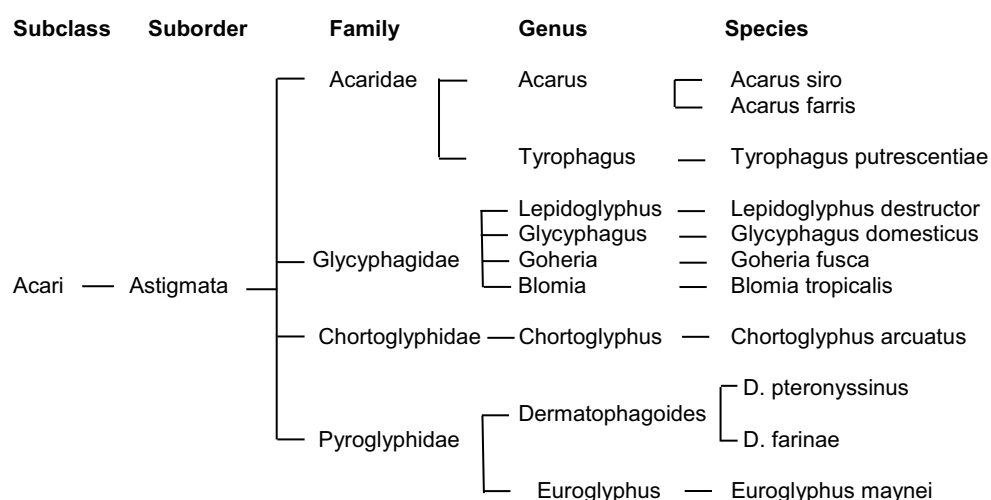
There is a strong cross reactivity among different storage mite species [9, 15]. Cross reactivity between storage mites and house dust mites (HDM) is reported with a wide range [9, 16, 17]. Nonetheless patients

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Fig. 1 Taxonomy of mites (adapted from van Hage-Hamsten et al. [5])



sensitized to house dust mites often have co-sensitization to storage mites [9, 18]. Data on nasal provocation or nasal challenge in patients sensitized to storage mites are scarce [19, 20]. For house dust mites there are more data pointing to an age dependency with younger children showing more positive challenges after positive SPT or specific IgE than the elderly [21–24].

The most significant allergens of these species are Lep d 2 of *L. destructor* and Tyr p 2 of *T. putrescentiae*. For *Acarus siro* so far only a single allergen (Aca s 13) has been identified and listed in the IUIS allergen nomenclature database (<http://www.allergen.org>) [25–28].

Objective

The objective of the present study was to characterize patients from a midwestern German city sensitized to storage mites. We wanted to evaluate co-sensitization with house dust mites and other allergens, correlation of intradermal testing and specific IgE testing and evaluate symptoms and point-in-time when symptoms were present in these patients. Also nasal provocation testing was to be evaluated.

Materials and methods

This study was performed in the Department of Otorhinolaryngology, Head and Neck Surgery of the University Medical Center Mainz, Germany. The database evaluated comprises 3997 patients with suspected allergic rhinitis who visited the allergy clinic. Patients' ages ranged from 0–88 years.

Patients were asked to fill in a standardized questionnaire according to Schultze-Werninghaus [29]. This included history of allergic diseases, affected relatives, questions concerning work environment and living quarters, animal contact, and food and drug allergies. To further specify their symptoms, patients were asked about seasonality and duration

of asthma, coughs, rhinorrhea, sneezing, nasal obstruction, eye symptoms such as tearing or itching, urticaria, swelling or itching of the mouth, tongue or pharynx, atopic eczema, gastrointestinal symptoms, reduced sense of smell and presence of chronic sinusitis.

Allergic rhinitis for storage mites (*Acarus siro*, *Tyrophagus putrescentiae* and *Lepidoglyphus destructor*), for house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and for mould (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Fusarium roseum*, *Penicillium notatum*, *Botrytis cinerea*) was diagnosed by intradermal testing ("intrakutan Testlösung" [intradermal test solution]; 500 biological units/ml, Allergopharma GmbH & Co. KG, Reinbeck, Germany) and in vitro testing of patients' sera for specific compound IgE antibodies. The other allergens were tested by standard array skin prick test (SPT) and included birch, alder, hazel, beech, rye, grass mix, ribwort, ambrosia, cat, dog (ALK Prick SQ 100 SQ-E/ml, ALK-Abelló, Wedel, Germany). Histamine served as a positive control and saline solution as a negative control. After 20 min, reactions in the SPT and intradermal test were recorded in four degrees of severity according to wheal size (0 for negative; 1 for a wheal of up to 3 mm; 2 for a wheal of 3 mm to 5 mm and 3 for a wheal of more than 5 mm). For evaluation of data a score of greater/equal 1 was deemed to be a positive result.

For in vitro testing, standard specific serum IgE determination was used (ImmunoCAP, Thermo Fisher Scientific, Freiburg, Germany). The measured units were divided into seven groups from 0 to VI. CAP classes of $\geq$ II were considered positive. For evaluation of the data, two consecutive CAP classes were taken together, so that four classes resulted ($0 \leq 0.35$ KU/l, $1 \hat{=} 0.36$ to 3.49 KU/l, $2 \hat{=} 3.50$ to 52.49 KU/l, $3 \hat{=} \geq 52.50$ KU/l).

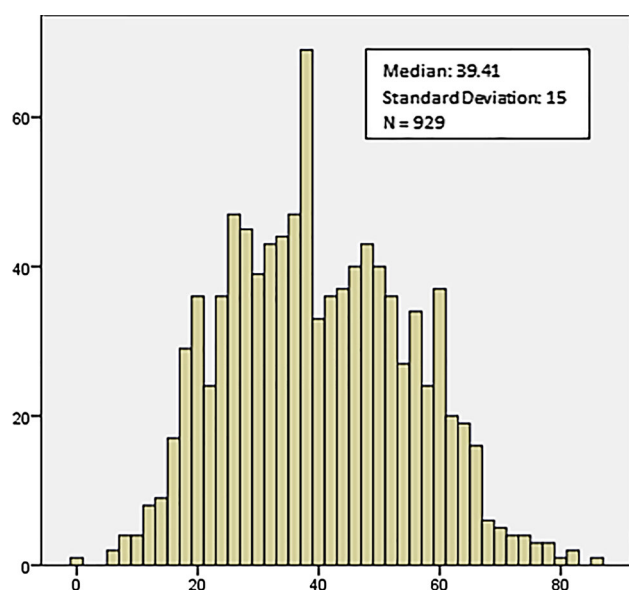


Fig. 2 Age distribution of subjects sensitized to storage mites

Statistics

A standard desktop PC with SPSS 23 software (IBM, Armonk, NY, USA) was used for the statistical evaluation. *P*-values of 0.05 were regarded as significant. No adjustment for multiple testing was performed. Therefore, only the error rate per comparison is controlled. Mean values and standard deviation were chosen for graphical representation of the results.

Symptoms and their seasonality from the questionnaire were scored binominally.

To describe the agreement of SPT, intradermal test and specific IgE test results Cohen's kappa was used.

For assessment of kappa, the classification proposed by Landis and Koch [30] was used.

For evaluation of the probability of symptoms, univariate logistic regression and multivariate logistic regression was performed leading to odds ratios. Also, for evaluation of the point-in-time symptoms which were reported by patients, logistic regression was performed. Odds ratio plots for representation of the results of logistic regression were generated at <https://www.statstodo.com> (Chinese University of Hong Kong, China), Venn diagrams were created at <https://www.meta-chart.com> (USA).

Results

Of the 3997 patients in the database 929 subjects (23.2%) were sensitized to storage mites. The age distribution of these patients is shown in Fig. 2. Mean age was 39.4 years, median age 38 years.

Fig. 3 depicts cross sensitization of storage mites with house dust mites. Interestingly in the study cohort slightly more subjects (929) were sensitized to storage mites (which amounts to 23.2% of subjects) than to house dust mites (915 or 22.8%). A total of 401 (10%) subjects were only sensitized to storage mites and 387 (10%) only to house dust mites, while 528 (13%) were sensitized to both mite groups. This means that 56% of all storage mite sensitized subjects were also sensitized to house dust mites and 57% of all house dust mite sensitized subjects were sensitized to storage mites.

When further breaking it down with cross tables the cross sensitization profiles of the three individual storage mites with the two house dust mite species were similar (Fig. 4, Table 1).

In all, 706 subjects in this cohort were sensitized to *Acarus siro* (17% of the cohort), 738 (18%) subjects

Fig. 3 Co-sensitization of storage mite (SM) and house dust mite (HDM) sensitized subjects

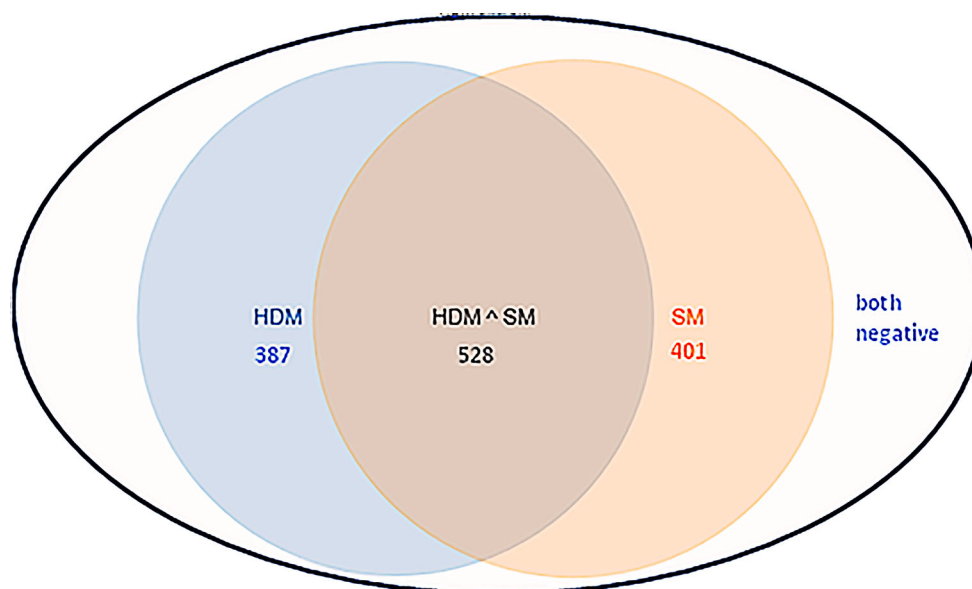


Fig. 4 Cross sensitization house dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronissimus*) and storage mite sensitized subjects

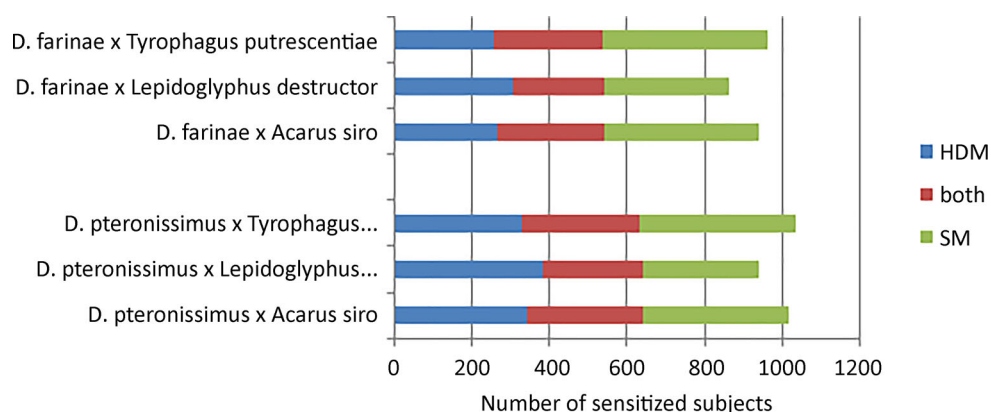


Table 1 Cross sensitization of house dust mite and storage mite sensitized subjects

	HDM (%)	Both (%)	SM (%)
<i>D. farinae</i> × <i>Tyrophagus putrescentiae</i>	256 (7)	280 (8)	425 (13)
<i>D. farinae</i> × <i>Lepidoglyphus destructor</i>	308 (9)	235 (7)	322 (10)
<i>D. farinae</i> × <i>Acarus siro</i>	266 (8)	275 (8)	401 (12)
<i>D. pteronissimus</i> × <i>Tyrophagus putrescentiae</i>	329 (10)	305 (9)	402 (12)
<i>D. pteronissimus</i> × <i>Lepidoglyphus destructor</i>	385 (12)	257 (8)	300 (9)
<i>D. pteronissimus</i> × <i>Acarus siro</i>	341 (10)	299 (9)	377 (11)
<i>HDM</i> house dust mites, <i>SM</i> storage mites			

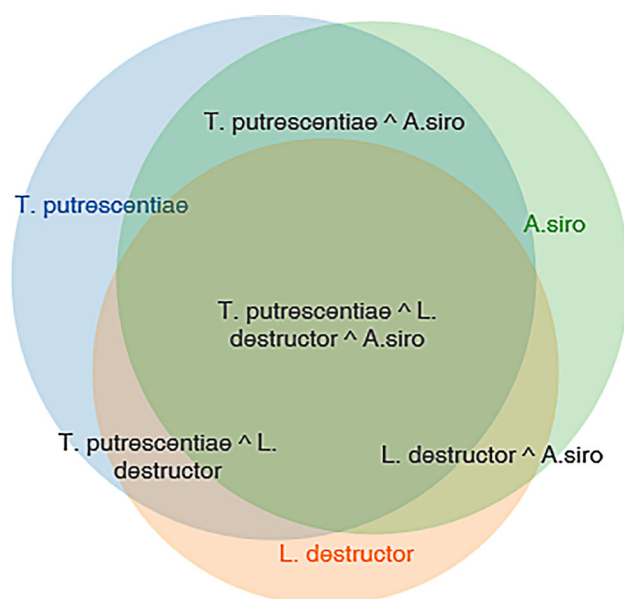


Fig. 5 Cross sensitization of storage mite sensitized subjects

were sensitized to *Tyrophagus putrescentiae* and 583 (14%) subjects were sensitized to *Lepidoglyphus destructor*. Fig. 5 and Table 2 depict cross sensitization of these groups: 417 (44%) patients were sensitized against all three species.

Comparing intradermal testing results to results from specific IgE testing showed little concordance with Cohen's kappa values of 0.08 or less (data not shown). As can be seen in Table 3 on the example of *T. putrescentiae* this was due to quite a number of patients showing sensitization in intradermal testing

Table 2 Cross sensitization of storage mite sensitized subjects

Storage mites	Number of subjects
<i>Lepidoglyphus destructor</i> × <i>Acarus siro</i>	467
<i>Tyrophagus putrescentiae</i> × <i>Acarus siro</i>	548
<i>Tyrophagus putrescentiae</i> × <i>Lepidoglyphus destructor</i>	475
<i>Tyrophagus putrescentiae</i> × <i>Acarus siro</i> × <i>Lepidoglyphus destructor</i>	417

Table 3 Cross table for *Tyrophagus (T.) putrescentiae* intracutaneous testing (IC) and *Tyrophagus putrescentiae* specific IgE

		<i>T. putrescentiae</i> ; specific IgE in pooled ImmunoCAP® classes				Total
		0	1	2	3	
<i>T. putrescentiae</i> ; IC, condensed wheal size	0	17	0	0	0	17
	1	122	20	13	0	155
	2	154	31	42	13	240
	3	96	36	56	16	204
Total		389	87	111	29	616

that could not be reproduced in specific IgE testing. Similar results were found for *A. siro* and *L. destructor*.

Sensitization to other allergens in these subjects was especially pronounced for grasses (45%) and spring bloomers (birch 42%, hazel 31%, alder 30%) as can be seen in Fig. 6.

Problems with nasal obstruction and reduced sense of smell were reported by more than 50% of subjects sensitized to storage mites. Other symptoms were described less frequently (Fig. 7).

Fig. 6 Co-sensitizations of storage mite allergic patients

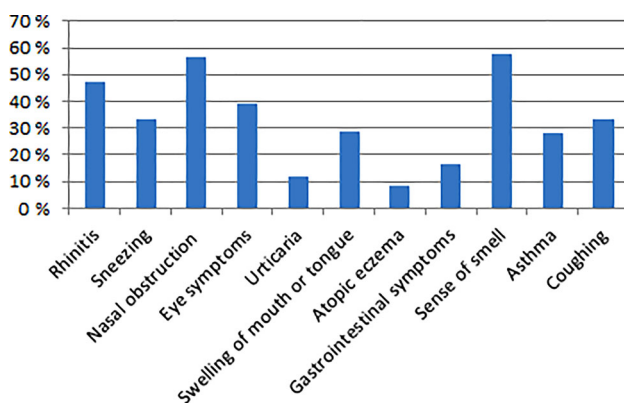
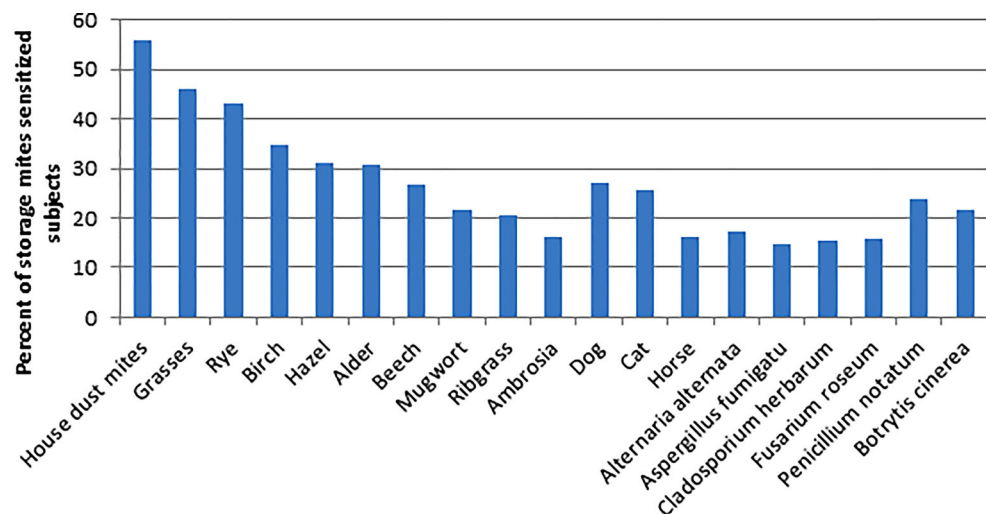


Fig. 7 Symptoms of storage mite sensitized subjects

To further evaluate the symptoms of these subjects in comparison to not storage mite sensitized subjects in the studied database we performed logistic regression analysis. Here we could include 3549 subjects. We found a significant association of storage mite sensitization with symptoms for atopic eczema, rhinitis, urticaria, and reduced sense of smell in comparison

to subjects not sensitized to storage mite. The occurrence of nasal obstruction as symptom was reduced in this group of subjects compared to subjects not sensitized to storage mites. (Fig. 8, Tables 4, 5 and 6). To further evaluate these findings we differentiated these subjects into those with symptoms of chronic sinusitis (1401 subjects) and those without symptoms of chronic sinusitis (1135 subjects). The other subjects could not be included due to missing data on chronic sinusitis. Here subjects with chronic sinusitis still had a significant probability of symptoms for rhinitis and urticaria and the probability of nasal obstruction was still significantly reduced. On the other hand in subjects without chronic sinusitis the probability to be symptomatic for nasal obstruction was not significantly reduced anymore. These subjects still had a significant probability for rhinitis, atopic eczema and reduced sense of smell.

The excess prevalence of symptoms in sensitized subjects compared to the non-sensitized subjects in the study population was most pronounced in summer and autumn (Fig. 9, Table 7).

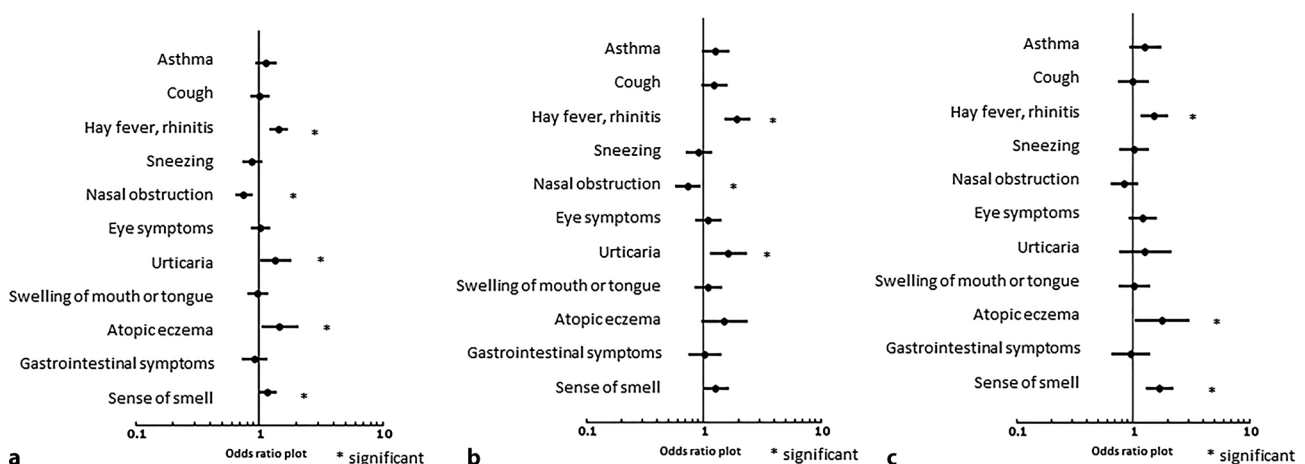


Fig. 8 a–c Probability of symptoms: **a** storage mite sensitized subjects without adjusting for sinusitis, **b** storage mite sensitized subjects with chronic sinusitis, **c** storage mite sensitized subjects without chronic sinusitis

Table 4 Probability of symptoms of storage mite sensitized subjects without adjusting for sinusitis

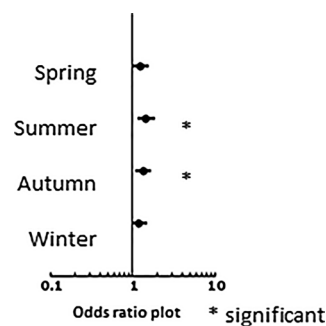
Symptom (without adjusting for sinusitis)	p-value	OR	95% confidence interval	
			Lower value	Upper value
Asthma	0.205	1.132	0.935	1.370
Cough	0.950	1.006	0.843	1.200
Rhinitis/rhinorhea	0.000	1.432	1.217	1.685
Sneezing	0.139	0.876	0.735	1.044
Nasal obstruction	0.000	0.745	0.640	0.866
Eye symptom	0.840	1.017	0.860	1.204
Urticaria	0.040	1.347	1.014	1.790
Swelling	0.722	0.967	0.801	1.166
Atopic eczema	0.027	1.464	1.045	2.051
Gastrointestinal symptoms	0.444	0.913	0.724	1.152
Reduced sense of smell	0.045	1.169	1.004	1.361
OR odds ratio				

Table 5 Probability of symptoms of storage mite sensitized subjects with chronic sinusitis

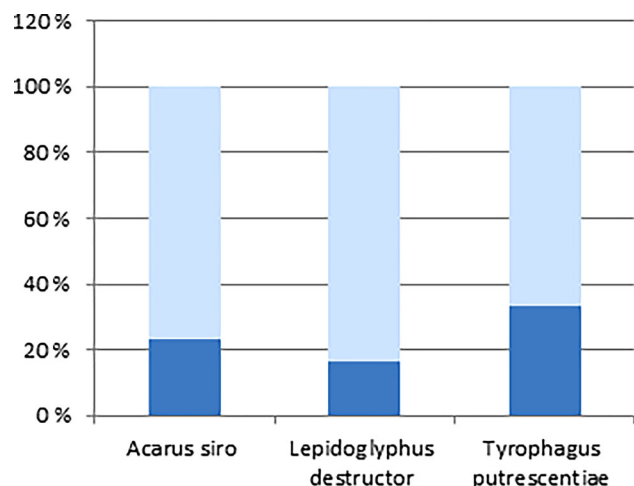
Symptom (Subjects with chronic sinusitis)	p-value	OR	95% confidence interval	
			Lower value	Upper value
Asthma	0.085	1.263	0.968	1.646
Cough	0.116	1.221	0.952	1.566
Rhinitis/rhinorhea	0.000	1.922	1.506	2.453
Sneezing	0.458	0.909	0.705	1.170
Nasal obstruction	0.013	0.730	0.570	0.935
Eye symptom	0.499	1.089	0.851	1.395
Urticaria	0.008	1.617	1.133	2.309
Swelling	0.513	1.092	0.839	1.420
Atopic eczema	0.083	1.487	0.950	2.327
Gastrointestinal symptoms	0.910	1.018	0.745	1.391
Reduced sense of smell	0.063	1.260	0.988	1.608
OR odds ratio				

Table 6 Probability of symptoms of storage mite sensitized subjects without chronic sinusitis

Symptom (Subjects without chronic sinusitis)	p-value	OR	95% confidence interval	
			Lower value	Upper value
Asthma	0.138	1.267	0.927	1.730
Cough	0.982	0.997	0.740	1.341
Rhinitis/rhinorhea	0.003	1.514	1.157	1.982
Sneezing	0.909	1.017	0.766	1.349
Nasal obstruction	0.197	0.841	0.647	1.094
Eye symptom	0.181	1.204	0.917	1.582
Urticaria	0.358	1.266	0.766	2.092
Swelling	0.878	1.024	0.757	1.386
Atopic eczema	0.036	1.763	1.039	2.992
Gastrointestinal symptoms	0.796	0.952	0.654	1.386
Reduced sense of smell	0.000	1.673	1.285	2.178
OR odds ratio				

**Fig. 9** Point of time of symptoms**Table 7** Point of time of symptoms

Time of year	p-value	OR	95% confidence interval	
			Lower value	Upper value
Spring	0.067	1.234	0.985	1.546
Summer	0.002	1.443	1.146	1.816
Autumn	0.009	1.332	1.075	1.650
Winter	0.104	1.185	0.966	1.453
OR odds ratio				

**Fig. 10** Nasal provocation in storage mite sensitized subjects

To evaluate the clinical significance of the high sensitization rates nasal provocation testing was performed in a small number of patients (59 subjects: 26 *A. siro*, 18 *L. destructor*, 15 *T. putrescentiae*). Of these a clinical relevant reaction could be seen in 23% (*A. siro*), 17% (*L. destructor*) and 33% (*T. putrescentiae*) (Fig. 10). Due to the small number a relevant bias cannot be excluded.

Discussion

In this study we describe sensitization patterns and symptoms in a large cohort of patients from midwestern Germany. The advantage of this study is the large number of patients tested for allergic rhinitis which should provide consistent testing results for skin tests and specific serum IgE as well as data on symptoms

and symptom duration through distribution of a standardized questionnaire.

The co-sensitization rates to house dust mites of 56% found here are within the wide range of so far reported co-sensitization rates between 46 and 85% [9, 17]. In children lower rates have been reported [31]. The three different storage mite species looked at did not differ from each other in their co-sensitization rate to house dust mites. Co-sensitization to other allergens was common, with grasses and tree pollen being the most relevant.

Cross-sensitization among storage mites showed some overlap between the different species with 44% of the study population being sensitized to all three species looked at. Arlin et al. and Griffin et al. showed that on a molecular basis there was little cross allergenicity the different storage mite species tested [1, 32]. Other studies also only showed a partial cross reactivity between the species [33].

In the study population there was little agreement of specific IgE testing and intradermal testing. When further analyzing this we found that a large portion of subjects were positive to storage mites in intradermal testing but had a CAP class of zero in specific IgE testing. Since we do not have sufficient data on provocation testing in these patients, we cannot differentiate whether this discrepancy is the result of overdiagnosis in intradermal testing or underdiagnosis in specific IgE testing.

The symptoms reported by the study population are as expected with nasal obstruction and hyposmia the most common symptoms. Asthma was reported by almost 30% of subjects which is in line with numbers previously reported [34]. These results might be confounded by polysensitization so that further analysis by logistic regression was performed.

Here we found that patients sensitized to storage mites had a significant risk of rhinitis/rhinorrhea and reduced sense of smell but interestingly also of urticaria and atopic eczema in comparison to their non-sensitized controls. On first view sensitization seemed to have a protective effect concerning nasal obstruction. In a stratified analysis this effect was only present in patients with comorbid chronic rhinosinusitis. The finding might be explained by the fact that subjects with chronic sinusitis are used to nasal obstruction and therefore do not have an additional burden concerning this symptom if they are sensitized or even allergic to storage mites. This might also explain why subjects with chronic sinusitis do not have an additional problem with their sense of smell whereas those without chronic sinusitis do show a significant probability of reduced sense of smell.

Nasal provocation testing was only performed in a minority of sensitized patients so that clinical significance may be biased by the small number of patients. If taken at face value sensitized patients were only allergic in 16–33% of cases depending on the underlying storage mite.

In conclusion, storage mite sensitization is relevant and should be part of standard sensitization testing. Cross-sensitization among storage mites is high, whereas cross-sensitization to house dust mites is present in about half of subjects. The main symptoms are rhinitis, nasal obstruction and hyposmia with chronic sinusitis playing a role in the perception of these symptoms. The clinical relevance of these sensitization rates has to be further evaluated since the portion of sensitized patients with actual storage mite allergy seems to be low as diagnosed per nasal provocation testing.

Conflict of interest T. Huppertz, I. Schmidtman, S. Becker and B.R. Haxel declare that they have no competing interests.

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