

Milk allergy is frequent in patients with chronic sinusitis and nasal polyposis

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ABSTRACT

Background: Chronic sinusitis and nasal polyps with subsequent nasal blocking, anosmia, and relapsing infections are frequent in the rhinological practice. Often, recurrent disease necessitates repetitive conservative therapy and surgical treatment (functional endoscopic sinus surgery). This study was initiated to scrutinize the relationship of wheat and milk allergies to chronic polypoid sinusitis (CPS) and recurrent disease.

Methods: Blood samples of 50 healthy controls and 50 patients with clinically and radiologically diagnosed CPS and nasal polyposis were screened for common food allergies including wheat and milk allergy. On inclusion into the study, none of the patients reported a symptomatic food allergy.

Results: Fifteen of 100 tested subjects (15%) revealed a previously undiagnosed allergy to inhalant (dust, rye, and pollens) and other food allergens (corn and egg white). Six of 50 patients (12%) with CPS exhibited a wheat allergy, and a milk allergy could be identified in 7 patients (14%). In the control group, seven healthy subjects (14%) showed a wheat allergy and no case of milk allergy could be identified ($p = 0.0125$).

Conclusion: In contrast to previous studies in other countries presenting a food allergy incidence of ~75% in patients with nasal polyposis, we could not show such a high incidence. In the group with chronic polyposis 14% of the patients were positive for milk allergy compared with none of the tested healthy subjects, resulting in a strong statistical significance. Therefore, we conclude that cow's milk but not wheat allergy might be a relevant pathogenetic entity in chronic nasal polyps.

(Am J Rhinol Allergy 25, e221–e224, 2011; doi: 10.2500/ajra.2011.25.3686)

Nasal polyps have a lifetime prevalence of ~4%, resulting in subjective and objective nasal obstruction, anosmia, and frontal cephalgia. Recurrent infections of the paranasal sinuses are the direct consequence of abnormal nasal ventilation. Chronic polypoid sinusitis (CPS) represents a common problem and is usually treated with local and systemic steroids and antiallergic medication. A large number of patients are nonresponsive to conservative therapy strategies or suffer a CPS relapse. If conservative therapy fails, surgical treatment is necessary requiring functional endoscopic sinus surgery. The operative procedure might be a routine surgery, but nevertheless can result in complications. Perioperative bleeding and injury of the orbit are deemed to be minor complication factors. Major complications such as penetration of the skull base, the internal carotid artery, and the optical nerve are more common in revision surgery. Consequently, CPS relapses in previously operated patients are more technically complicated to treat and should be avoided. Aside from commonly tested inhalant allergens (e.g., pollens and dust), data are sparse. This prospective study aimed to identify certain ingested allergens associated with recurrent nasal polyposis.

However, genuine food allergies are relatively rare compared with food intolerances. The number of patients who believe themselves to have a food allergy clearly differs from those who actually suffer from a true food allergy.¹ In the United States, ~25% of the population believe they have a food allergy, although the prevalence is supposed to range from 1 to 3% in adults and 3 to 8% in infants.²

Nasal blocking due to CPS is a common problem and although the cause still remains unclear, allergies seem to be associated with the development of nasal polyps. In 2000, a study from Singapore described a strong correlation of certain food allergies to CPS, with 81% of patients with nasal polyps having a positive intradermal food allergy test. In the control group only 11% showed allergic reactions, which resulted in a high correlation between CPS and food allergy.³

In addition, Dogru *et al.* initiated a study in Turkey presenting patients with a high prevalence of food allergy. Of 34 patients with nasal polyps, 25 (73.5%) had a positive food allergy prick test compared with healthy subjects, which was highly significant ($p < 0.001$).⁴ In the United Kingdom 70% of patients suffering from nasal polyps presented positive skin tests for different types of food including wheat, tomato, potato, and milk, which was significantly higher than in a healthy control group ($p = 0.006$).⁵ When dealing with chronic inflammatory disorders of the head and neck with special regard to the upper aerodigestive tract, food allergies need to be considered constantly.⁶

Similar allergens affect the nose, paranasal sinuses, and the skin. The most common antigens associated with food allergy in patients with atopic dermatitis are shrimp (54%), egg white (43%), wheat (42%), and peanuts (41%), as described by a group in China.⁷ In recent years, soy has also become a commonly known allergen provoking atopic dermatitis.⁸ In addition, hereditary factors may play a role in the development of nasal polyps as well.⁹

Why nasal polyps arise remains unclear. Allergic genesis, hereditary aspects, and aspirin intolerance are often being discussed. Nonetheless, patients present with CPS without the typical inhalant allergies, without nasal polyps in the family history, and their recurrent disease remains unexplained. This study evaluated patients with a CPS without any known inhalant, wheat, or milk allergy to uncover any correlation between these entities.

PATIENTS AND METHODS

Fifty CPS patients (30 male and 20 female patients) aged between 20 and 87 years (mean, 44 years) received functional endoscopic sinus surgery at the Department of Otorhinolaryngology, Head and Neck Surgery, of the Medical University of Vienna after failure of conservative therapeutic strategies. Data are shown in Table 1. Blood samples were taken after informed consent had been given according to the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical University of Vienna (EK 567/2008).

All patients were subjected to detailed history and clinical examination including nasal endoscopy and a CT scan. Total IgE and allergen-specific IgE were evaluated in a prospective study between April 2009 and November 2010. All patients included suffered from CPS and had surgical treatment at least once. Two weeks before and

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The authors have no conflicts to declare pertaining to this article

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Table 1 Demographic data of patients (*n* = 50) and healthy controls (*n* = 50)

Patients	50	
Sex	Female, 20	Male, 30
Age	Mean, 44 yr (range, 20–87 yr)	
Healthy controls	50	
Sex	Female, 25	Male, 25
Age	Mean, 44 yr (range, 23–71 yr)	

at the time of blood sample collection the patients had no antiallergic or steroid therapy. None of the patients had cystic fibrosis or diabetes mellitus. Neither patients with chronic sinusitis without nasal polyps nor patients <18 years if age were included. Serum concentration of allergen-specific IgE to wheat, milk protein, α -lactalbumin, and β -lactoglobulin were measured by radioallergosorbent test (RAST) fluorescence enzyme immunoassay. Specific IgE levels of >0.35 kilounits of antibody per liter (kUA/L) were considered positive. In addition, total IgE levels were measured and enhanced levels were declared as >100 kU/L.

Table 2 Results of RAST against wheat and milk allergy in 50 patients

Patient	IgE Total (<100 kU/L)	Wheat (kUA/L)	Milk Protein	α -Lactalbumin	β -Lactoglobulin
1	1061	2.71/2	8.3/3	1.89/2	0.41/1
2	Normal	Neg	Neg	Neg	Neg
3	949	Neg	Neg	Neg	Neg
4	Normal	Neg	0.65/1	0.85/2	Neg
5	140	Neg	Neg	Neg	Neg
6	Normal	Neg	Neg	Neg	Neg
7	Normal	Neg	Neg	Neg	Neg
8	918	Neg	Neg	Neg	Neg
9	237	Neg	Neg	Neg	Neg
10	242	Neg	Neg	Neg	Neg
11	367	Neg	0.59/1	Neg	Neg
12	Normal	Neg	0.48/1	0.75/2	Neg
13	Normal	Neg	Neg	Neg	Neg
14	n.d.	1.04/2	Neg	Neg	Neg
15	n.d.	Neg	Neg	Neg	Neg
16	Normal	Neg	Neg	Neg	Neg
17	n.d.	Neg	Neg	Neg	Neg
18	n.d.	Neg	Neg	Neg	Neg
19	Normal	Neg	Neg	Neg	Neg
20	Normal	Neg	Neg	Neg	Neg
21	n.d.	Neg	Neg	Neg	Neg
22	Normal	Neg	Neg	Neg	Neg
23	Normal	Neg	Neg	Neg	Neg
24	Normal	1.39/2	Neg	Neg	Neg
25	913	47.8/4	Neg	Neg	Neg
26	n.d.	Neg	Neg	Neg	Neg
27	n.d.	Neg	Neg	Neg	Neg
28	152	Neg	Neg	Neg	Neg
29	n.d.	Neg	Neg	Neg	Neg
30	n.d.	Neg	Neg	Neg	Neg
31	n.d.	Neg	Neg	Neg	Neg
32	Normal	Neg	Neg	Neg	Neg
33	105	Neg	Neg	Neg	Neg
34	Normal	Neg	0.49/1	Neg	Neg
35	1955	1.31/2	0.45/1	Neg	Neg
36	220	Neg	Neg	n.d.	n.d.
37	121	Neg	Neg	Neg	Neg
38	Normal	Neg	Neg	Neg	Neg
39	n.d.	Neg	Neg	Neg	Neg
40	n.d.	Neg	Neg	Neg	Neg
41	n.d.	Neg	Neg	Neg	Neg
42	n.d.	0.37/1	Neg	Neg	Neg
43	n.d.	Neg	Neg	Neg	Neg
44	n.d.	Neg	Neg	Neg	Neg
45	n.d.	Neg	Neg	Neg	Neg
46	n.d.	Neg	Neg	Neg	Neg
47	Normal	Neg	Neg	Neg	Neg
48	1582	Neg	Neg	Neg	Neg
49	324	Neg	0.58/1	Neg	Neg
50	Normal	Neg	Neg	Neg	Neg

kUA/L = kilounits of antibody per liter; Neg = Negative; n.d. = not determined; RAST = radioallergosorbent test.

Comparison was made with 50 healthy controls without any signs of sinusitis including 25 male and 25 female patients. The mean age was 44 years with a range from 23 to 71 years. None of the healthy subjects suffered from chronic sinusitis or nasal polyposis.

Statistical Methods

Statistical analysis was performed with the open source package R-project.¹⁰ The number of allergic patients in both CPS and control groups was compared using a Fisher's exact test. The ratios of participants with positive and negative wheat/milk protein levels were compared between the two groups using a Fisher's exact test. To accommodate multiple testing, Bonferroni correction was used.

RESULTS

The blood samples of 50 patients and 50 healthy subjects were evaluated for wheat and milk allergy. RAST against wheat, milk protein, α -lactalbumin, and β -lactoglobulin as well as total IgE level was performed.

Six (12%) of 50 patients tested showed positive RAST against wheat. Four of these patients had a moderate, one a slight, and one a distinct allergy (47.8 kUA/L). Seven patients presented with milk allergy (14%) in whom six had slight values and one a moderate value. Three of these seven patients with proven milk allergy had a positive RAST test against α -lactalbumin and one against β -lactoglobulin. The one patient with the moderate milk allergy (8.3 kUA/L) had slightly to moderately positive values for α -lactalbumin and β -lactoglobulin. Of all 50 CPS patients, two presented a combination of wheat and milk allergy. Data are shown in Tables 2 and 3.

The number of allergic patients did not differ significantly between the polyposis (22%, 11 of 50) and the control (14%, seven of 50) group (Fisher's exact test, $p = 0.436$; Bonferroni corrected, $p = 0.871$; odds ratio [OR] = 1.71; 95% CI = 0.546–5.801). The ratio of wheat-positive patients in the polyposis group (12%, 6 of 50) did not differ significantly from the control (14%, 7 of 50) group (Fisher's exact test, $p = 1$; Bonferroni corrected, $p = 1$; OR = 0.858; 95% CI = 0.218–3.26).

Regarding milk protein, seven of 50 (14%) polyposis patients were positive, compared with none in the control group. Therefore, we could show that milk allergy is significantly more frequent in patients with CPS than in the control group, resulting in a strong significance (Fisher's exact test, $p = 0.0125$; Bonferroni corrected, $p = 0.037$; OR = ∞ ; 95% CI = 1.56– ∞).

In addition, we could make primary diagnoses in 12 patients revealing a variety of inhalant and food allergies and one patient, animal allergy. Nine patients presented inhalant allergies such as pollens, rye, or ragweed. One patient had developed a low-level allergy to corn and one to milk and eggs.

DISCUSSION

The etiologic factors causing CPS are still controversially discussed. Hereditary reasons, a blocked ostiomeatal unit, nasal trauma, different inhalant and food allergies, aspirin intolerance, and cystic fibrosis are taken into account.

Approximately 40 years ago, Caplin *et al.* evaluated 3000 patients with evident allergies, but only 0.5% of them had nasal polyps.¹¹ Settupane *et al.* found more nasal polyps in nonallergic than in allergic patients in his study of 6000 patients,¹² and Slavin *et al.* assumed described no pathogenetic connection between allergy and nasal polyps.¹³ In contrast, more recent articles describe a strong correlation between allergy and CPS. Pang *et al.* found a significantly increased incidence of food allergies in patients with (81%) and without (11%) nasal polyps in 2000.³ Three years later, Dogru *et al.* published data with 25 positive food allergy tests in 34 patients with nasal polyps (73.5%) and six positive tests of 20 controls (30%) reaching high significance ($p < 0.001$).⁴ Additionally, Collins *et al.* found similar results with a majority of allergic patients within a patient collective

Table 3 Results of RAST against wheat and milk allergy in 50 healthy subjects

Patient	IgE Total (<100 kU/L)	Wheat (kUA/L)	Milk Protein
1	173	15.4/3	Neg
2	16.4	Neg	Neg
3	50.3	Neg	Neg
4	3.05	Neg	Neg
5	66.1	Neg	Neg
6	16.1	Neg	Neg
7	11.5	Neg	Neg
8	10.6	Neg	Neg
9	15.4	Neg	Neg
10	39.5	Neg	Neg
11	144	0.97/2	Neg
12	94.5	Neg	Neg
13	10	Neg	Neg
14	5.55	Neg	Neg
15	23.4	Neg	Neg
16	4.83	Neg	Neg
17	56.7	Neg	Neg
18	3.67	Neg	Neg
19	11.5	Neg	Neg
20	14.1	Neg	Neg
21	41.6	Neg	Neg
22	104	Neg	Neg
23	14.7	Neg	Neg
24	54	Neg	Neg
25	1528	Neg	Neg
26	49.8	Neg	Neg
27	1843	11.7/3	Neg
28	31.6	0.44/1	Neg
29	3.56	Neg	Neg
30	35.9	Neg	Neg
31	119	Neg	Neg
32	18.7	Neg	Neg
33	21.4	Neg	Neg
34	241	Neg	Neg
35	72.6	Neg	Neg
36	365	0.64/1	Neg
37	290	1.33/2	Neg
38	39	Neg	Neg
39	34.6	Neg	Neg
40	3.03	Neg	Neg
41	11.8	Neg	Neg
42	<2	Neg	Neg
43	183	Neg	Neg
44	61.5	Neg	Neg
45	4.48	Neg	Neg
46	n.d.	Neg	Neg
47	20.2	Neg	Neg
48	265	Neg	Neg
49	162	8.46/3	Neg
50	5.89	Neg	Neg

kUA/L = kilounits of antibody per liter; Neg = Negative; n.d. = not determined; RAST = radioallergosorbent test.

suffering from nasal polyps.⁵ Interestingly, inhalant allergens were more infrequent and showed no evidence of significance in patients with nasal polyps tested by skin-prick test.⁵

Besides the allergies discussed previously, different etiologic factors such as chronic infections and osseous obstructions might cause CPS. On the other hand, studies have shown polyp cell populations with >60% eosinophils, mast cells, and activated T cells.¹⁴ These

findings beg the question of whether allergic stimulus plays a significant role in CPS pathogenesis. In addition to allergic components, vascular endothelial growth factor is highly expressed locally, which leads to neoangiogenesis and proliferation of nasal polyps.¹⁴

The fact that some patients suffer from recurrence of disease requiring multiple surgical interventions could be explained by a propagated intolerance to aspirin.¹⁵ In Finland, the overall aspirin intolerance was 5.7% in 1999.¹⁶ The incidence of aspirin intolerance has been shown to range from 0.6 to 2.5% in the general population¹⁷ and 36 to 96% patients with proven aspirin intolerance have nasal polyps.¹⁸ However, in some cases no intolerance to aspirin can be determined and other possible factors including perennial allergens must be investigated. Pang *et al.* concluded that aspirin intolerance is overestimated and the role of food hypersensitivity might be underestimated in the genesis of nasal polyps.³

Patients with atopic dermatitis show high association with food allergies. The most commonly detected allergies are shrimp (54%), egg white (43%), wheat (42%), and peanuts (41%). Allergy to cow's milk was observed in ~28% of patients with eczema⁷ and the prevalence of cow's milk protein allergy in children is stated to be 2–7.5%.^{19,20} There is a close association between atopic diseases and food allergies, as mentioned by Pyrhönen *et al.* in an epidemiologic study conducted among 3800 children in Finland.²¹ In addition, the development of food allergies seems to have hereditary components, because the incidence for a food allergy was threefold higher in children with both parents presenting an allergy compared with nonallergic control parents. In addition, the risk for developing a food allergy was twice as high, if only one parent showed allergies when compared with two healthy parents.²¹

In summary, six of the 50 patients suffering from nasal polyps showed wheat allergy and seven showed milk allergy. In the control group, wheat allergy was observed in seven healthy subjects (14%) and none had milk allergy. This correlation of milk allergy patients and healthy subjects was strongly significant.

We therefore conclude that no IgE-mediated wheat allergy is responsible for CPS, but milk allergy seems to be a possible risk factor for developing CPS. Consequently, a diet avoiding cow's milk might prevent the development of nasal polyps.

In addition, food intolerances, which are not IgE mediated, could be associated with nasal polyps; however, intolerances can only be proven by abstinence techniques and the patient's compliance in random food avoidance is limited. The experience during this study showed that the majority of patients were reluctant to participate in an allergen-avoiding diet and seldom considered such a diagnostic strategy even before the result of the RAST test.

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