The Role of Allergy Therapy in Chronic Rhinosinusitis: A Systematic Review

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Abstract The role of allergy in chronic rhinosinusitis (CRS) remains controversial. The objectives of the review were to determine if atopy plays a role in CRS, and to determine if allergy treatment impacts patient outcome. We screened 1,755 articles, resulting in 37 studies, of which 7 were prospective. No randomized controlled trials examining the benefit of immunotherapy in CRS were found in the literature. The study populations for the majority of the studies available were highly selected, evaluating patients failing medical therapy and often requiring endoscopic sinus surgery (ESS). Evidence from these studies suggests a high prevalence of atopy in CRS patients with a possible role of food allergy in CRS pathophysiology. Five of the 7 cohort studies in this review did not show a correlation between atopy and post-surgical outcome in CRS patients requiring ESS.

Keywords Atopy · Allergic rhinitis · Chronic rhinosinusitis · Nasal polypsis · Immunotherapy · Asthma

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disorder without a currently known etiology. CRS is heterogeneous with a spectrum of phenotypes and is considered multifactorial. Allergic rhinitis (AR) has been linked to CRS pathology not only because the two disorders coexist but are also characterized by the common denominator of inflammation. The correlation between AR and CRS is controversial and the data remains mixed. Increasingly, CRS is recognized as an inflammatory disorder with associated innate and adaptive immune dysfunction. Recent literature suggesting a local IgE hypersensitivity in the patient with negative allergy testing provides insight into the complexity of the disorder and may explain response to anti-IgE therapy in “non-allergic patients” [1•]. In a previous publication therapeutic strategies for AR in controlling inflammation were proposed to also be beneficial in CRS patients especially in patients with both disorders [2•]. While the pathophysiology of CRS is certainly diverse and frequently elusive, symptom-specific therapy and avoidance in those patients with concomitant allergic disease has been proposed to potentially ameliorate potential drivers of inflammation. This systematic review examines the evidence regarding the role of atopy in CRS severity and treatment outcome.

Definitions and Epidemiology of Atopy

The definition of atopy varies in the literature and sometimes used interchangeably with allergy. In general, most would agree that atopy is a tendency to produce IgE to allergens and is a characteristic phenotype of diseases such as AR or as a disease modifier. The prevalence of atopy in

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Fig. 1 Literature search flow

the general population is increasing. In the U.S. the prevalence of atopy based on the National Health and Nutrition Examination Survey 2005–2006 was 43.7 %, an increase of 2–5.5 times from several decades earlier [3•, 4]. A recent GA²LEN survey showed that 56.7 % of those reporting symptoms that fulfilled the EP³OS criteria for CRS also reported symptoms of allergy [5•]. The significance of these findings in the context of clinical relevance, i.e., symptom severity, quality of life outcomes, and treatment implications, however, is unclear.

Systematic Review of Atopy and CRS

The objectives of this review were to determine whether an association exists between atopy and chronic rhinosinusitis, as well as to determine if there is an impact of allergy treatment for patients with chronic rhinosinusitis. Prospective studies and controlled trials published in the English language evaluating adults or children with CRS with or without nasal polyps (NPs) in the setting of atopy (inhalant and food allergies) were included. Retrospective

studies and reviews were excluded. Figure 1 shows a schematic of the literature search and selection.

Outcome Measures

Outcome measures including symptom scores, radiographic severity, incidence of patients requiring surgery, and surgical outcome were analyzed. Prevalence of atopy in CRS and the prevalence of aspirin-exacerbated respiratory disease (AERD) in comparison to control populations, if available, were also evaluated.

Search Methods for Identification and Selection of Studies

A literature review was conducted by two authors (JIC and SL) using PubMed for articles from 1985 through September 2012. A Medical Subject Headings search using the subject headings “rhinitis, allergic, seasonal” or “rhinitis, allergic, perennial” or “food hypersensitivity” and “sinusitis” or “nasal polyps” yielded 426 abstracts for review. An additional PubMed free text search using the terms “allergy,” “chronic sinusitis,” “rhinosinusitis,” “nasal polyps,” “allergic rhinitis,” “atopy,” “immunotherapy,” and “food allergy” was conducted. This search strategy yielded an additional 1,329 abstracts, for review for a total of 1,755 abstracts. Reference lists from identified publications were scanned to identify further trials, which were missed by the initial search criteria, yielding an additional two abstracts. Quality of the studies was assessed, inclusion criteria applied independently, and any difference in opinion about which studies to include in the review was resolved by discussion and consensus. Thirty-seven studies met the inclusion criteria.

Data Collection and Analysis

A standardized data extraction form was utilized and each article underwent duplicate review. Differences in opinion were resolved by discussion and consensus.

A total of 1,755 papers were identified, and after appropriate exclusion 37 papers were included in the review. No randomized controlled studies were available in the literature. Prospective and controlled studies were included and all retrospective studies and reviews excluded. Twenty-one articles supported a role of atopy in CRS while 16 papers showed no association.

Prevalence of Atopy in CRS Patients

The prevalence of atopy reported in patients with CRS and/or nasal polyposis varied widely, 16–85 % for inhalant

sensitivities and 12–81 % for food sensitivities. The study populations were highly selected with many of the studies enrolling patients who had failed medical therapy or already undergone endoscopic sinus surgery. Dust mite and mold sensitivities as well as food sensitization were more common in controlled studies that suggested a role for atopy in CRS. It was found that prevalence measurements varied based on the particular time point at which a study was conducted as well as the population studied. The majority of studies, however, did not consistently provide prevalence measurements in the context of normative data for that time point and population. The studies included in this review also showed variability in allergy testing methods including skin prick, intradermal, and measurements of serum-specific IgE as well variability in the diagnosis of CRS (Table 1).

Studies Supporting a Role for Atopy in CRS Patients

A total of 21 studies showed a role for atopy in patients with CRS or nasal polyposis, with 1 prospective cohort study (evidence level 2b), 16 case-control studies (evidence level 3b), and 4 case-series (evidence level 4). The one cohort study evaluated the role of allergy treatment including immunotherapy on CRS outcome in pediatric patients and found that medical therapy before surgery with topical nasal steroid sprays, oral antihistamines, and immunotherapy (in 25 % of patients) improved the surgical success rate at a 1 year follow up from 64 to 84 % [6]. The authors proposed that treatment of allergy before surgery could help improve outcome. In this study, however, the authors describe that all patients underwent allergy evaluation but did not describe their specific method of allergy testing.

In a recent study, Lin et al. [7•] found a higher rate of surgery in CRS patients with AR, as well as increased symptom severity and likelihood of medication use. There was a prevalence of 65 % of atopy in the CRS patients compared to 18 % in the control group. Other studies have also showed that the presence of allergy increased symptom severity [8–11]. These studies utilized validated symptom scores including the SF-36, rhinosinusitis disability index (RSDI), and the sinonasal outcome test (SNOT-20).

The majority of studies found an association with perennial allergen sensitivities and CRS or nasal polyposis, specifically dust mite [10, 12•, 13–15] and mold [16, 17]. In a Spanish study evaluating 121 patients with nasal polyps, 63 % had positive skin prick testing compared to 31 % of controls. *Dermatophagoides pteronyssinus* was the most common allergen eliciting a response [13]. The authors suggested a possible IgE-mediated hypersensitivity

Table 1 Prospective studies evaluating the role of atopy in CRS

Author(s)	Years	Study design/ level of evidence	Follow-up period	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Prevalence of atopy in CRS/NP	Symptom severity	CT scan severity	ESS outcome	Correlation
<i>Studies supporting a role for atopy in CRS</i>												
Ramadan and Hinerman [6]	2006	Cohort/ 2b	12 months	U.S.	Sinus CT	Unknown	141 children failing medical therapy s/p ESS	55 %	No significant difference between allergic and non-allergic patients.	Not studied	84 % atopic patients success after ESS compared to 62 % without treatment	Allergy treatment before surgery improved surgical success rate at 1 year follow-up 84 %, compared to 62 % who were not treated
<i>Studies showing no supporting role for atopy in CRS</i>												
El Sharkawy et al. [23•]	2012	Cohort/ 2b	28 months (mean)	Egypt	Clinical history (12 weeks persistent symptoms), sinus CT, nasal endoscopy (if available)	Clinical history with SPT and elevated serum IgE (inhalants)	87 children failing medical therapy undergoing surgery, 45 patients with AR, 36 patients without AR, 6 patients with NP	51.7 %	No significant difference.	Significant improvement in LMS for all 87 patients.	87.5 % success rate CRS with AR compared to 85.7 % CRS without AR	No difference between the presence of allergy in success rate of ESS for CRS
Katotomichelekis et al. [24]	2009	Cohort/ 2b	6 months	Greece	NP stage III Malm classification, Sinus CT	Clinical history with SPT (inhalants)	116 patients with Stage III NP s/p ESS	53.4 %	Not studied	Not studied	No difference in olfactory function between AR and no AR, AERD patients had worse outcomes	AR patients have similar post-op improvement compared to non-AR CRS patients. AERD patients have significantly worse olfactory outcome
Bonfils and Malinvaud [22]	2008	Cohort/ 2b	Mean 5.8 years, minimum 2 years after ESS	France	Nasal endoscopy, sinus CT	In vitro test (inhalants)	22 CRSwNP with allergy, 41 CRSwNP without allergy; both after undergoing ESS	34.90 %	Initial severity of symptoms nearly identical in both groups. No difference found after surgery	Not studied	No difference in symptom severity between both groups found	No difference in symptoms after surgery of patients with nasal polyps with or without allergy

Table 1 continued

Author(s)	Years	Study design/ level of evidence	Follow-up period	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Prevalence of atopy in CRS/NP	Symptom severity	CT scan severity	ESS outcome	Correlation
Matsuwaki et al. [25]	2008	Cohort/ 2b	5 years	Japan	Clinical history, Nasal endoscopy, Sinus CT, Questionnaire	Patient- reported symptoms and total IgE	65 CRS patients s/p ESS	55.3 %	Not studied	LMS in CRS recurrence vs. no recurrence was not significantly different (10.7 vs. 9.1)	16.1 % had recurrence of CRS in the 5 years post- ESS, allergy was not a significant factor	No correlation between AR and recurrence of CRS
Bonfils et al. [27]	2006	Cohort/ 2b	1 year	France	Nasal endoscopy, Sinus CT	In vitro test (inhalants)	180 NP patients in symptom severity study, 74 NP in medical treatment study	19.5 % of 180, 16.2 % of 74	No difference in clinical global severity index between groups	Not studied	Not studied	Presence of allergy did not change initial symptoms in patients with polyposis. Presence of allergy did not change symptoms in patients with polyposis after 1 year medical treatment.
Smith et al. [26]	2005	Cohort/ 2b	At least 1 year, mean 1.4 years	U.S.	Rhino-sinusitis task force criteria, Sinus CT	Clinical history	119 CRS patients undergoing sinus surgery	35 %	No difference in CSS or RSDI in allergy versus no allergy	No difference in allergy versus no allergy LMS.	No difference in allergy versus no allergy degree of improvement	History of allergy had no impact on pre- or postoperative CT, endoscopy, or QOL

in the development of polyps. A study of CRS patients who failed medical therapy, found that 82 % were positive on skin prick testing with higher rates of asthma, and multiple allergen sensitivity especially to dust mite and ragweed in CRS with NP patients compared to controls [12•].

A correlation has been suggested with NPs and food allergy and four case–control studies were included in our review. A higher rate of milk allergy was seen in CRS with NP compared to controls, whereas no difference was seen for wheat sensitization [18•]. Patients undergoing surgery for NPs were also more likely to have positive food SPT compared to controls (70 vs. 34 %). The prevalence of positive inhalant SPT, however, was not significantly different between patients with NP compared to controls (43 vs. 48 %) [19]. A Turkish study showed a higher rate of food sensitization in NP patients in comparison to controls (73.5 vs. 15 %) with the most common reactions to onion, oat, grapefruit, plum, buckwheat, and apple [20]. Other food reactions included wheat, potato, and tomato in a similar study from Singapore, which found a significantly higher prevalence of food sensitivity in NP patients compared to controls (81 vs. 11 %) [21]. The authors in this study concluded that the presence of salicylates in food may not contribute to the pathogenesis of NPs since only 1 patient reacting to the salicylate-containing foods tested, tomato and/or pea, was found.

IDT to food allergens has been shown to be more sensitive than SPT for detecting atopy, perhaps due to a bigger allergen dose to register a response [22]. The pathophysiology of food allergy reactions remains unclear with type II, III, and IV delayed hypersensitivity reactions also proposed to contribute to chronic inflammation. It is interesting to note that the majority of study patients did not report a history of food hypersensitivity [21, 22, 23•, 24].

None of the studies evaluated whether exposure to the foods found positive on testing resulted in worsening symptoms, CT scan scores, post-surgical outcome, or whether elimination diets led to resolution of inflammation.

Studies Showing no Role of Atopy in CRS Patients

A total of 16 studies showed no association between atopy and CRS or nasal polyps, including 6 cohort studies, 2 case–control studies, and 8 case-series (Table 2). Five of the prospective studies found no differences between the presence of atopy, post-operative improvement, and symptoms after endoscopic sinus surgery [22, 23•, 24–26]. In a recent study by El Sharkawy et al. there was no difference in surgical success rate after a mean follow-up of 28 months in pediatric patients with or without allergy. The definition of success was based on improvement in sinus CT 8 weeks post-operatively, nasal exam, and an un-validated symptom

survey. Olfactory outcome measured by Sniffin' Sticks in a study of 116 patients with NPs found no difference between allergic and non-allergic groups, although patients with AERD had a worse olfactory outcome [24]. Similarly, a French study evaluating symptom severity after ESS reported no difference after a minimum 2 year follow-up (mean 5.8 years) between patients with and without atopy [22]. This study used an un-validated symptom severity survey measuring degree of nasal obstruction, rhinorrhea, and loss of smell. Rather than a history of allergy or total IgE, local eosinophilia was the most predictive parameter for recurrent disease in a 5 year follow-up study of 65 patients with CRS who had undergone ESS. In this study, however, antigen-specific IgE was not measured and a history of allergy was obtained via an unvalidated questionnaire. Atopy also did not appear to play a role in CRS patients when examining medication usage including topical nasal steroid sprays, irrigations, and oral corticosteroids over a period of 1 year [27]. In this study, nasal function was evaluated on a 3-point scale evaluating nasal obstruction, anterior/posterior rhinorrhea, facial pain, and loss of smell.

Of the 17 studies that evaluated symptom severity, 10 studies reported no difference in symptom scores between atopic and non-atopic groups [6, 13, 22, 23•, 26, 27, 28•, 29–31, 32•]. Only 2 of the 10 studies, however, used a validated symptom survey (RSDI, Chronic Sinusitis Survey, or Visual Analogue Scale) with the remaining studies utilizing un-validated symptom surveys, a clinical history of allergy or self-reported symptoms to determine allergic symptoms rather than an objective measure of atopy [25, 26].

Ten of the 12 studies examining CT scan severity showed that the presence of atopy did not appear to significantly influence Lund-Mackay scores (LMS) [8, 12•, 25, 26, 29, 30, 32•, 33–35]. Although no difference between endoscopic or LMS of patients with NPs were seen there were higher levels of IL-4, IL-5, IL-6, and eosinophils in atopic NP patients compared to non-atopic patients [32•]. In a case series, Robinson et al. [11] showed that there was no significant difference in rate of revision surgery in atopic compared to non-atopic patients (38 vs. 45.2 %), but there was a modest increase in mean LMS in atopic patients. Another case series showed an association between CT stage and mean end point with increased skin sensitivity correlating with more severe disease on CT [9].

Atopy, CRS, and AERD

Since patients with AERD have increased severity of disease with high recurrence of polyps, the role of atopy in these studies was evaluated to determine potential confounding of data. Eleven of the studies reported the prevalence of AERD [20, 24, 25, 27, 29, 31, 35, 37–40]. The

Table 2 Case–control and case-series studies between AR and CRS

Author(s)	Years	Study design/ level of evidence	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Controls	Prevalence of atopy in CRS/NP	Prevalence of atopy in controls	Correlation
<i>Studies supporting a role for atopy in CRS</i>										
Lin S et al. [7]	2012	Case–control/3b	United States	Rhinosinusitis task force guidelines	Physician diagnosis of AR or prior positive allergy testing	35 w/o AR and CRS, 65 w/AR and CRS	82 w/o AR and w/o CRS, 18 w/AR and w/o CRS	65 % of CRS patients	18 % controls	Higher rate of surgery in CRS with AR, no difference in symptom severity of AR and CRS compared to no AR and CRS
Peric et al. [32]	2012	Case-series/4	Serbia	Clinical evidence of polyposis, nasal endoscopy, sinus CT	SPT and in vitro (inhalants)	30 patients with NPs requiring surgery (13 allergic and 17 non-allergic)	No controls	NS	NS	Allergy did not play a role in symptom severity, endoscopic, or radiographic severity of NPs but there were higher levels of IL-4, IL-5, IL-6, and eosinophils in atopic NPs compared to non-atopic NPs
Lill et al. [18]	2011	Case–control/3b	Austria	Clinical history, nasal endoscopy, sinus CT	In vitro (wheat, milk protein, alpha-lactalbumin, beta-lactoglobulin)	50 CRSwNP s/p ESS	50 controls without sinusitis (however not clearly defined)	12 % wheat, 14 % milk	14 % wheat, 0 % milk	Higher rate of milk allergy in CRSwNP compared to controls
Tan et al. [12]	2011	Case–control/3b	United States	Nasal endoscopy, Sinus CT	Clinical history with SPT or IDT (inhalants)	62 CRSwNP, 63 CRSSNP	50 AR and NAR w/o evidence of CRS on CT scan	85.5 % of CRSwNP, 79.4 % of CRSSNP	72 % controls (54.3 % of NHANES)	Higher rate of atopy in CRS patients failing sinus surgery
Munoz del Castillo et al. [13]	2009	Case–control/3b	Spain	Nasal endoscopy, EP3OS classification	SPT (inhalants)	190 NP patients	190 controls w/o sinusitis or NPs	63.20 %	31.10 %	63.2 % positive in NP compared to 31.1 % controls
Alobid et al. [8]	2006	Case-series/4	Spain	Nasal endoscopy, sinus CT	SPT (inhalants)	109 NP patients, 35 with atopy, 74 without atopy	No controls	32 % in NP with atopy versus 68 % NP without atopy	NS	Atopy increased the impact on quality of life in those with nasal polyposis
Collins et al. [19]	2006	Case–control/3b	England	Nasal endoscopy, sinus CT	IDT to food panel, 14-day food diary and SPT to inhalant panel	40 NP refractory to medical therapy undergoing ESS	21 non-atopic controls based on nasal symptoms	70 % food, 43 % inhalant	34 % food, 48 % inhalant	Patients with nasal polyps and positive food IDT were more likely to have negative inhalant SPT compared to controls. The prevalence of positive inhalant SPT was not different between polyps and controls
Van Lancker et al. [38]	2005	Case–control/3b	United States	Nasal endoscopy	SPT (inhalants)	25 NP patients, 50 AR patients	14,367 National Health and Nutrition Examination Survey (NHANES) II who underwent SPT	NP patients 72 % to perennial, 84 % to seasonal; AR patients 96 % to perennial, 86 % to seasonal	NHANES II 7.6 % to perennial, 17.7 % to seasonal	The prevalence of atopy in NP was higher than in the general population

Table 2 continued

Author(s)	Years	Study design/level of evidence	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Controls	Prevalence of atopy in CRS/NP	Prevalence of atopy in controls	Correlation
Dogru et al. [20]	2003	Case-control/3b	Turkey	Nasal endoscopy	SPT (foods)	34 NP patients with previous negative inhalant SPT, no history of food allergy, or atopic disease	20 healthy volunteers	73.50 %	15 %	Association between asymptomatic IgE-mediated food hypersensitivity and nasal polyposis
Asero and Bottazzi [17]	2001	Case-control/3b	Italy	Clinical evidence of polyposis	SPT (inhalants)	68 NP	36 with chronic sinusitis, 1128 with respiratory allergy	63 %	17 %	Sensitivity to perennial allergens was highly prevalent in nasal polyposis
Asero and Bottazzi [16]	2000	Case-control/3b	Italy	Clinical evidence of polyposis	SPT (inhalants)	20 severe polyposis	409 with respiratory allergy	45 % (mold)	11 % (mold)	45 % severe polyposis patients sensitive to mold in comparison to controls, <i>Candida albicans</i> most common
Krouse [9]	2000	Case-series/4	United States	Clinical history, AAO-HNS criteria, nasal endoscopy, sinus CT	Allergy questionnaire, IDT	48 CRS patients	No controls	NS	NS	Correlation between CT score and mean end point as well as symptom scores. Increased skin end point titrations scores correlated with advanced CT stage
Pang et al. [21]	2000	Case-control/3b	Singapore	Clinical evidence of polyposis	IDT (foods)	80 NP	36 controls	81 %	11 %	Higher prevalence of food allergy in NP patients compared to controls
Berrettini et al. [14]	1999	Case-control/3b	Italy	Clinical history, nasal endoscopy, sinus CT	Clinical history, SPT (inhalants)	40 with PAR	30 controls (patients with dizziness undergoing head CT)	NS	NS	Dust mite sensitivity correlates with pathologic CT. 67.5 % of AR patients had sinus inflammation on CT versus 33.4 % of controls
Pumhirun et al. [41]	1999	Case-control/3b	Thailand	Clinical evidence of polyposis	SPT (inhalants)	40 patients with NPs	30 controls	60 %	20 %	Patients with NPs have higher prevalence of atopy than controls
Sin et al. [37]	1997	Case-control/3b	Turkey	Clinical history, evidence of polyposis, sinus X-ray	SPT, in vitro (inhalants)	95 patients with NPs	20 healthy volunteers	66 %	NS	Allergy thought to play a role in NP with dust mite allergy most common. 66 % of NP had SPT positive and 45 % both SPT and RAST positive
Newman et al. [10]	1994	Case-series/4	United States	Clinical history, sinus CT	Questionnaire, In vitro (inhalants), eosinophil count	104 CRS patients undergoing sinus surgery	No controls	20 %	NS	Antigen-specific IgE and eosinophilia correlate with increased severity on sinus CT

Table 2 continued

Author(s)	Years	Study design/level of evidence	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Controls	Prevalence of atopy in CRS/NP	Prevalence of atopy in controls	Correlation
Armenaka et al. [35]	1993	Case-control/3b	United States	Clinical history, sinus CT	SPT (inhalants)	21 Severe sinusitis (12 with NP), 21 mild sinusitis, 21 rhinitis	21 volunteers	33 % to dust mite in severe sinusitis, 24 % in mild sinusitis, 15 % in rhinitis	19 %	Dust-mite IgG correlated with sinusitis severity, however, most patients (76 %) were not mite-allergic based on skin testing
Perkins et al. [42]	1989	Case-control/3b	United States	Clinical history, nasal endoscopy	SPT, IDT, and, in vitro (inhalants)	12 NP, 10 AR no NP, 10 NAR no NP	10 control (without nasal polyps or known atopy)	58.3 % (SPT), 50 % (in vitro)	30 % (SPT), 10 % (in vitro)	Patients with NPs had increased markers for atopic disease (SPT, specific IgE in serum, nasal secretions, and nasal polyp fluid) compared to controls
Freudenberger et al. [15]	1988	Case-control/3b	United States	Clinical history, sinus X-ray	IDT, In vitro (inhalants)	22 CRS patients	22 controls (without history of allergy or asthma)	68 % (IDT, dust mite), 41 % (in vitro, dust mite)	6 % (IDT, dust mite), 5 % (in vitro, dust mite)	Significantly higher prevalence of dust mite sensitivity in CRS compared to controls
<i>Studies showing no supporting role for atopy in CRS</i>										
Ahmadiatshar et al. [28•]	2012	Case-series/4	Iran	Nasal endoscopy	Clinical history with SPT (inhalants)	250 with AR or asthma, 60 patients with NP	No controls	22.9 % (NPs)	No controls	No difference in SPT allergen positivity comparing AR patients with and without polyps
Pearlman et al. [34]	2009	Case-series/4	United States	Task force on rhinosinusitis, sinus CT	SPT (inhalants)	40 CRSwNP, 66 CRSsNP	No controls	49.00 %	No controls	Prevalence of CRSwNP similar between atopic and nonatopic patients (38 vs. 37 %)
Gelincik et al. [30]	2008	Case-series/4	Turkey	Joint task force on practice parameters, nasal endoscopy, sinus CT	Clinical history in conjunction with SPT (inhalants)	115 persistent rhinitis patients, 52 with CRS	No controls	65.30 %	No controls	For the development of CRS, AR does not seem to be a more predisposing factor than NAR
Erbek et al. [29]	2007	Case-series/4	Turkey	Clinical history, nasal endoscopy, sinus CT, questionnaire	SPT (inhalants)	83 NP patients (no surgery in past year)	No controls	66.30 %	No controls	Presence of inhalant allergy in NP patients did not effect symptom scores, polyp size, LMS, or recurrence of disease
Leo et al. [40]	2007	Case-series/4	Italy	Clinical history meeting two of major criteria (nasal discharge, obstruction, and cough) × 12 weeks	SPT and UniCap (inhalants)	351 children meeting clinical criteria for CRS	No controls	29.90 %	31.8 % prevalence of allergy in children from Italian arm of ISAAC II study	Children with CRS have a comparable rate of allergic sensitization to inhalant allergens compared with general public
Robinson et al. [11]	2006	Case-series/4	Australia	Clinical evaluation, sinus CT	In vitro (inhalants)	127 CRSsNP, 66 CRSwNP	No controls	30.10 %	No controls	No impact of atopy on disease severity and need for surgical revision but has a modest effect on the radiological severity of the disease

Table 2 continued

Author(s)	Years	Study design/ level of evidence	Study origin	CRS diagnostic method	AR diagnostic method	Study population	Controls	Prevalence of atopy in CRS/ NP	Prevalence of atopy in controls	Correlation
Tezer et al. [43]	2006	Case- series/4	Turkey	Clinical history, sinus CT	SPT (inhalants)	339 CRS	No controls	62.80 %	No controls	CT scan findings were comparable between allergic and non-allergic CRS patients
Voegels et al. [39]	2001	Case- control/ 3b	Brazil	Nasal endoscopy	Clinical history, SPT, serum IgE measurement (inhalants)	39 NP patients s/p ESS	11 controls (non- allergic, normal endoscopy)	33 %	0 %	In patients with NPs, the presence or absence of allergy did not correlate with the presence of asthma or ASA intolerance
Hoover et al. [33]	1997	Case- series/4	United States	Clinical history, sinus CT	Clinical history, in vitro test (inhalants)	80 CRS patients	No controls	40 %	No controls	Eosinophil count more predictive of CRS severity rather than asthma or atopy
Keith et al. [31]	1994	Case- control/ 3b	Canada	Physical exam of nasal cavity for polyp size	SPT (ragweed)	16 with NP allergic to ragweed, 16 with NP not allergic to ragweed, 16 allergic to ragweed with no NP	16 controls (non- allergic)	Defined by study as ragweed positive	Defined by study as ragweed negative	Seasonal allergy exposure in CRSwNP does not affect disease severity

prevalence was reported between 2 and 21.9 % and did not appear to differ between patients with atopy, non-allergic rhinitis, nasal polyposis, and controls. Although patients with AERD demonstrate increased rates of recurrence of disease and severity of symptoms, atopy did not appear to play a significant role in these patients.

Allergy Testing and Immunotherapy in CRS Patients

Based on current evidence and guidelines, allergy testing in the management of CRS patients is optional [36]. The evidence in this systematic review suggests that allergy and CRS commonly co-exist and therefore allergy testing and immunotherapy, if appropriate, is warranted for the treatment of AR. Whether this treatment impacts CRS outcome is unclear. No randomized controlled trials investigating the role of immunotherapy in CRS treatment have been performed. With the absence of evidence and heterogeneity of data, no formal recommendation can be made regarding immunotherapy in CRS patients.

Symptoms of allergy and rhinosinusitis often overlap and it is often difficult to distinguish one from the other clinically. In our practice, allergy evaluation and treatment is recommended for all CRS patients who have undergone an initial trial of medical therapy without success, and immunotherapy is recommended for patients with inadequate relief with environmental controls in conjunction with medical therapy or with symptoms for at least 6 months of the year. Patient who also have a clinical history of food intolerance or hypersensitivity are also tested for food allergy and counseling is provided on elimination or avoidance if appropriate.

Conclusion

The evidence suggesting a role for atopy in CRS is limited, although it appears that the two disorders commonly co-exist and food allergy may play a role. Only one prospective study evaluating the potential role for immunotherapy in patients with AR and CRS met criteria for inclusion suggesting that allergy immunotherapy helps improve post-surgical outcome. The studies evaluated in this review also suggest that atopy does not play a significant role in CT scan severity or post-surgical outcome in patients with CRS or nasal polyposis. Future study is needed to determine the etiology for the higher prevalence of food allergy in patients with CRS and whether allergy immunotherapy or avoidance can improve patient outcome.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- Of importance
- Of major importance

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