

Clinical aspects of the link between chronic sinonasal diseases and asthma

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ABSTRACT

Chronic sinonasal diseases (CSDs) are common comorbidity of asthma. The aim of this study was to assess comprehensively CSD in a population of asthma patients and determine whether the clinical factors in both diseases were related to each other. Eighty adult stable asthmatic patients with sinonasal symptoms (SNSs) of 3 months and who were nonresponsive to aggressive medical treatment were prospectively investigated. All patients underwent a detailed ear, nose, and throat examination and were evaluated by paranasal sinus computed tomography (PNS-CT). The severity of asthma was compared with SNS scores (SNSs) and sinonasal involvement on PNS-CT. Asthma was severe in 12.5%, moderate in 55%, and mild in 32.5% of cases. There were 15 (18.7%) patients in stage 0, 16 (20%) patients in stage 1, 21 (26.2%) patients in stage 2, and 28 (35%) patients in stage 3 according to PNS-CT scoring. There was no correlation between asthma severity and CT stages, total opacification scores (TOSs), anatomic variations, and SNSs. Although SNSs were similar in patients with nasal polyps (NPs) and without NPs, patients with NPs showed significantly higher TOSs and CT stages ($p < 0.05$). The presence of NPs and age and duration of disease were related to severity of asthma ($p < 0.05$). Nonatopic asthmatic patients had both more severe asthma ($p = 0.05$) and more extensive CT findings ($p = 0.01$). The use of clinical symptoms alone is not very reliable in predicting the presence or severity of CSD. Therefore, SNSs should be supported with objective criteria such as nasal endoscopy and PNS-CT scan. Furthermore, sinonasal involvement may exist independently from severity of asthma.

(Allergy Asthma Proc 27:510–515, 2006; doi: 10.2500/aap.2006.27.2914)

Chronic sinonasal diseases (CSDs), with or without nasal polyposis (NP), and asthma are common diseases of the respiratory tract. The prevalence of asthma, chronic rhinosinusitis (CRS), and NP in the general population is 3–15%, 15–18%, and 0.2–4.3%, respectively.^{1–10} A relationship between asthma and CSD has long been recognized.^{4,5,7,9,11–19} Several studies have shown that CSD could worsen asthma and may contribute to asthma-related complications.^{4,5,11–19} In asthmatic patients with CSD, severe asthma symptoms have been reported to improve after the treatment of CSD, regardless of whether the treatment was administered medically or surgically.^{4–6,10,12–15,17,18,20–22}

Although clinical evidence is accumulating that chronic sinonasal problems exacerbates lower airway diseases, more direct and objective studies are needed to elucidate the role of CSD. The abundance of etiologic factors and the fact that different etiologic factors pose different prognoses make it difficult to perform a precise evaluation of the asthmatic patients with CSD. Moreover, asthmatic patients may not be aware of

upper respiratory tract involvement because of scarce nasal complaints in CSD. Previous reports have been concerned mainly with the effect of treatment of CSD on the improvement of asthma. However, such points as nature and extension of disease and the criteria associated with their evaluation have not been addressed adequately. The aim of this study was to assess CSD comprehensively in a population of asthma patients and determine whether the clinical factors in both diseases were related to each other.

MATERIALS AND METHODS

Patients

This study involved 80 asthmatic patients with chronic sinonasal symptoms (SNSs) and who attended the outpatient allergy–asthma clinic of the university hospital (Ankara University School of Medicine, Department of Respiratory Diseases, Allergic Diseases Division) between June 2003 and February 2004. It was designed prospectively to evaluate asthmatic patients with respect to SNSs and paranasal sinus–computed tomography (PNS-CT) findings.

Asthma was diagnosed and classified according to the criteria of the Global Initiative for Asthma 2002 consensus report.²³ Asthma medications consisted of inhaled corticosteroids, long-acting β_2 -agonists, leukotriene modifiers, and as-needed short-acting β_2 -agonists. No patient had taken systemic steroids. In

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addition, no patients were treated with allergen immunotherapy.

Asthmatic patients who had SNSs during the last 3 months were evaluated. Eighty of these patients were nonresponsive to medical treatment and were included in the study and went through PNS-CT examination. Any patient with systemic diseases such as tuberculosis, sarcoidosis, Wegener's granulomatosis, or pregnancy was excluded from this study.

Definitions for rhinosinusitis were made according to a consensus report²⁴: (1) acute (presumed bacterial) rhinosinusitis, (2) CRS without nasal polyps (CRSsNP), (3) CRS with nasal polyps (CRSwNP), and (4) allergic fungal rhinosinusitis. The patients with acute (presumed bacterial) rhinosinusitis or allergic fungal rhinosinusitis were excluded from this study. The patients were diagnosed with CRS based on the criteria of the Academy of Otolaryngology–Head and Neck Surgery Rhinosinusitis Task Force (1997).²⁵ The symptoms and findings of nasal endoscopy and PNS-CT were used for classification. CRS diagnosis was given if the patients had 12 weeks of persistent symptoms and signs or four or more episodes per year of recurrent acute rhinosinusitis each lasting 10 days, in association with persistent changes on CT scans after 4 weeks of medical treatment without intervening acute infection. Medical treatment consisted of four groups of drugs, which were used simultaneously after diagnostic nasal endoscopy: group 1, 4 weeks of antibiotics (amoxicillin-clavulanate, macrolide with combined ornidazole); group 2, 10 days of anti-inflammatory drugs (naproxen-sodium, etodolac, and nimesulide); group 3, 7 days of topical and/or oral decongestants (pseudoephedrine, xylometazoline, and oxymetazoline); group 4, 4 weeks of topical steroid (fluticasone propionate). If there was no opacification on CT scans, only a rhinitis diagnosis was given. In this group, allergic rhinitis diagnosis was given if the patients had atopy. According to definitions, the patients were divided into two groups in this study: CRS and rhinitis. The CRS group included both CRSsNP and CRSwNP.

Symptoms and findings of both upper and lower respiratory systems were investigated. All of the patients were asked specific questions regarding the history of wheezing or asthma, use of medications, duration of upper and lower airway symptoms, progress of disease, past sinus operations or procedures, and the presence of other illnesses. A brief history of drug and food allergy; seasonal variation or relation to allergen exposure in symptoms; and information on age, sex, and smoking habits also were obtained from each patient.

Atopic status was determined by means of skin testing. Skin-prick tests were applied with a lancet, using glycerinated allergen extracts (Stallergenes S.A., Antony, France). The test panel consisted of 25 com-

mon inhalant allergens including grass, tree and weed pollens, *Alternaria* and *Cladosporium* molds, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* dust mites, dog and cat animal danders, and cockroaches. Histamine (10 mg/mL) and phenolated glycerol-saline were used as a positive and negative control, respectively. Reactions were measured after 15 minutes. A test was considered positive if it produced a wheal with a mean diameter (mean of longest and midpoint of the perpendicular diameters) at least 3 mm greater than the saline control. Atopy was defined as the presence of a history and positive skin test response to at least one inhalant allergen.

Diagnostic nasal endoscopies were performed by a 2.7- or 4.0-mm rigid 0° or wide-angle 30° Karl-Storz endoscopes with and without using topical decongestants in all patients. PNS-CT examinations were done in the same institutions without using contrast material after the medical treatment by exclusion of any intervening acute infection. Coronal plane sections were taken.

Evaluation

Questionnaire on SNS. The common sinonasal complaints such as nasal discharge, nasal obstruction, nasal itching/sneezing, postnasal drainage, snoring/sleeping with an open mouth, facial congestion/pain/pressure fullness, loss of smell, headache, earache/pressure, halitosis, dental pain, cough, fever/fatigue, and frequent upper respiratory infection were questioned at least two times. The patients were asked to grade their symptoms between 0 and 3 according to severity (0, none; 1, mild; 2, moderate; and 3, severe), except for smell disorders (hyposmia and anosmia). Absence of smell disorders, hyposmia, and anosmia were scored as 0, 1, and 2, respectively. Total SNS score (SNSS) was derived by counting how many of 14 symptoms the patient's noted on the questionnaire. The range of possible scores was 0–41. The patients were evaluated by two different methodologies based on CT findings: staging and opacification scoring systems.

Staging System. The patients were evaluated using the following stages: stage 0, no opacification in any sinuses; stage 1, unilateral or bilateral, opacification in only the ostiomeatal region, opacification in the ostiomeatal region and an adjacent sinus, or opacification in only one sinus without any opacification in the ostiomeatal region; stage 2, unilateral or bilateral opacification in the ostiomeatal region and in more than one adjacent sinus or opacification in more than one adjacent sinus without any opacification in the ostiomeatal region; stage 3, unilateral or bilateral opacification in all sinuses.²⁶

Table 1 Characteristics of patients

	Rhinitis (n = 15)	CRS		p Value
		CRSsNP (n = 40)	CRSwNP (n = 25)	
Age, mean $\pm$ SEM (yr)	42 $\pm$ 2.9	44.15 $\pm$ 2.02	46.96 $\pm$ 2.09	0.437
Gender (F/M)	12/3	32/8	16/9	0.309
Duration of asthma (yr; mean $\pm$ SEM)	11.27 $\pm$ 2.78	11.25 $\pm$ 1.79	15.16 $\pm$ 2.58	0.392
Atopy [n (%)]	9 (60%)	12 (30%)	7 (25%)	0.078
History of drug allergy [n (%)]	2 (13.3%)	4 (10%)	9 (36%)	0.028
Previous sinonasal operation [n (%)]	2 (13.3%)	2 (5%)	16 (64%)	0.001
Presence of anatomic variations (n)	14	32	16	0.086
Severity of asthma (n)				
Mild (n)	8	14	4	
Moderate (n)	7	19	18	
Severe (n)	—	7	3	
Mean severity of asthma $\pm$ SEM	2.47 $\pm$ 0.13	2.83 $\pm$ 0.11	2.92 $\pm$ 0.13	0.102
Upper airway symptom scores (mean $\pm$ SEM)	12.93 $\pm$ 1.70	13.08 $\pm$ 1.02	14.84 $\pm$ 1.46	0.540
Total opacification scores (mean $\pm$ SEM)	0	9.57 $\pm$ 1.13	16.36 $\pm$ 1.44	0.001

CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; n = number of patients; F = female; M = male.

Opacification Scoring System. This system grades the extent of soft tissue disease on each of the PNSs (maxillary, frontal, sphenoid, anterior, and posterior ethmoids) on both sides. Opacification score was determined for each sinus as follows: 0, none; 1, involvement of $\leq 25\%$ of the sinus; 2, involvement of 25–75% of the sinus; and 3, involvement of $\geq 75\%$ of the sinus. Total opacification scores (TOS) range from 0 to 30. This scoring system was modified from those used by April *et al.*²⁷ Ostial complex anatomic variations such as septal deviation, concha bullosa, paradoxical middle turbinate, curved uncinate process, pneumatized uncinate process, overpneumatized or prolapsed bulla ethmoidalis, overpneumatized agger nasi cell, and Haller cell were determined also on PNS-CT scans.

Statistical Analysis

Comparisons were statistically analyzed by chi-square, Kruskal-Wallis, Mann-Whitney *U*, Tukey test, and logistic regression analysis. Spearman's correlation coefficient test was used also to determine the relationship between asthma severity and upper airway symptom score, CT score, and anatomic variations in PNSs. All data were expressed as mean $\pm$ SEM. A value of $p < 0.05$ was accepted as significant.

RESULTS

Of the 80 asthmatic patients, 25% (20/80) were male patients and 75% (60/80) female patients, with a mean age of 44.6 $\pm$ 11.8 years (range, 14–76 years). Charac-

Table 2 Anatomic variations of 80 patients

Anatomic Variations	n*	%
Overall	62	77.5
Septal deviation	43	53.8
Concha bullosa	29	36.2
Paradoxical middle turbinate	12	15.0
Curved uncinate process	4	5.0
Pneumatized uncinate process	3	3.7
Over pneumatized/prolapsed bulla ethmoidalis	8	10.0
Overpneumatized agger nasi cell	10	12.5
Haller cell	1	1.2

*Total number of patients with at least one anatomical variation is 62.

teristics of patients are shown in Table 1. Severity of asthma was classified as 32.5% (26/80), mild intermittent, and persistent asthma; 55% (44/80), moderate persistent asthma; and 12.5% (10/80), severe persistent asthma. Mean duration of asthma was 13.1 years (1–50 years).

Thirty-five percent (28/80) of the patients were atopic. The mean SNSS was 13.6 $\pm$ 6.7 (2–33). Patients were staged according to the PNS-CT as 18.8% (15/80), stage 0; 20% (16/80), stage 1; 26.2% (21/80), stage 2; and 35% (28/80), stage 3. TOSs were between 0 and 30 with a mean score of 9.9 $\pm$ 8.5 and ostiomeatal anatomic variations were detected in 77.5% (62/80) of the patients (Table 2), in whom 30 (37.5%) of them had

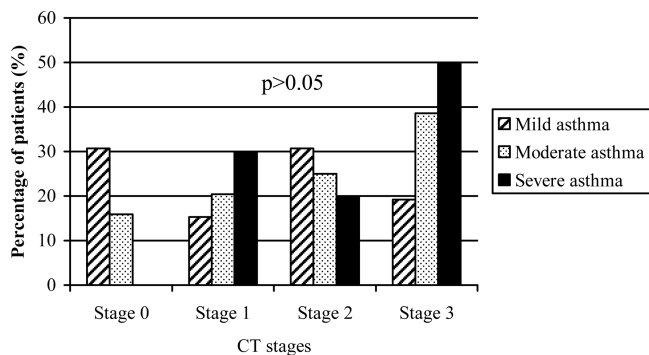


Figure 1. Relationship between severity of asthma and sinonasal disease on PNS-CT scan

more than one anatomic variation. Nineteen percent (15/80) and 81% (65/80) of the patients were diagnosed with rhinitis and CRS, respectively. NP was observed in 31.2% (25/80) of the patients. Patients with NP were mostly nonatopic (72% versus 28%).

Comparison of Parameters

Asthma Severity. There was no correlation between asthma severity and gender, smoking, or familial atopy. Both age and duration of asthma were significant predictors of asthma severity ($p = 0.005$ and $p = 0.003$, respectively). History of drug allergy was significantly higher in severe asthmatic patients ($p = 0.016$). Asthma was more severe in nonatopic patients ($p = 0.05$), as well as in those with NP ($p = 0.03$). Among patients with NP, 84% were diagnosed with moderate to severe persistent asthma. SNSSs were not correlated with asthma severity ($p > 0.05$). In addition, TOSs and anatomic variations on CT scan did not differ in terms of asthma severity; but all severe asthmatic patients had sinonasal involvement on CT scan and 50% of them were in stage 3. The relationship between severity of asthma and sinonasal disease on PNS-CT stages was shown in Fig. 1 ($p > 0.05$).

PNS Imaging. TOSs were significantly correlated to staging on PNS-CT ($p = 0.001$). There was no correlation between CT staging and age, gender, smoking, or duration of asthma. Furthermore, CT stages were not correlated with SNSS ($p > 0.05$).

There was a significant relationship between CT stages and atopic status. Nonatopic patients showed more advanced stages (stage 3) on PNS-CT when compared with atopic patients (44.2% versus 17.9%; $p = 0.049$; Fig. 2). The mean CT stage was lower in atopic patients than in the nonatopic patients (1.32 ± 0.21 versus 2.02 ± 0.15 , respectively; $p = 0.007$). TOSs were also higher in nonatopic patients (mean TOS, 11.50 ± 1.17 versus 6.93 ± 1.53 ; $p = 0.021$). Moreover, extensive sinonasal involvement on PNS-CT was detected in nonatopic patients with NP when compared with

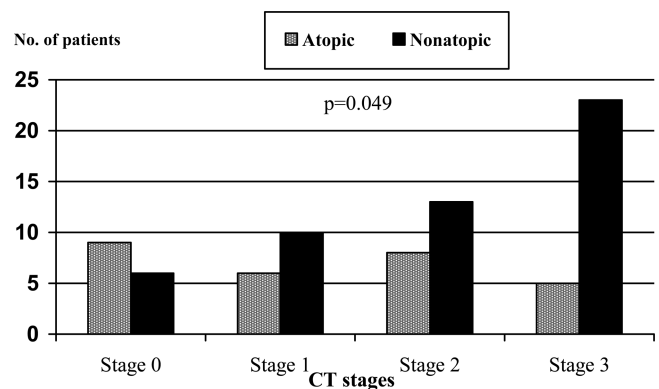


Figure 2. Comparison of severity of sinonasal disease on PNS-CT in atopic and nonatopic patients.

Table 3 Comparisons between atopy and asthma severity and SNSSs and TOS

Patient Status	No. of patients (n)	SNSS [Mean $\pm$ (SD)]	TOS [Mean $\pm$ (SD)]
Nonatopic	52	13.5 (6.5)	11.5 (8.4)*
Atopic	28	13.8 (7.1)	6.9 (8.1)
Asthma severity			
Mild intermittent and persistent	26	13.1 (7.8)	8.4 (9.1)
Moderate persistent	44	13.4 (6.0)	10.4 (8.3)
Severe persistent	10	15.6 (6.8)	11.4 (8.1)

* $p = 0.01$ TOS; nonatopic patients versus atopic patients.

atopic patients ($p = 0.02$). In addition, patients with NP showed more advanced stages on PNS-CT (68% of patients were in stage 3, 28% of patients were in stage 2, and 4% of patients were in stage 1) when compared with patients without NP (mean CT stage, 2.64 ± 0.11 versus 1.38 ± 0.15 ; $p = 0.001$).

SNSS. SNSSs did not change according to the atopic status ($p = 0.84$). In addition, there was no correlation between SNSSs and TOSs, staging on PNS-CT, and presence of anatomic variations ($p > 0.05$). SNSSs were not different between patients with and without NP (14.84 ± 1.46 versus 13.04 ± 0.86 ; $p > 0.05$), whereas TOS on PNS-CT was significantly higher in patients with NP than in those without NP (16.36 ± 1.44 versus 6.96 ± 1.01 ; $p < 0.05$). Comparison between these variables was given in Table 3.

DISCUSSION

As previously described and mainly provided by epidemiologic data, CRS and asthma are frequently associated in the same patient.¹⁴ However, doubts still remain as to whether a causal relationship exists where CRS worsens bronchial asthma.^{1,13,14} Several studies

have shown that asthma is aggravated by coexisting CRS.^{5,11,17,19} The most possible direct relationship between CRS and asthma is provided by studies that show significant improvement in asthma symptoms when CRS is appropriately treated.^{5,6,9,2-22} Moreover, SNSs commonly occur in asthmatic patients,^{18,19,28} and several studies showed that patients with severe asthma had more extensive sinonasal disease on CT scans.^{12,29-31} However, there are conflicting reports about the relationship between SNSs and CT findings. Authors generally have observed poor correlation and others reported that CT scan results were correlated to the clinical scores.^{12,13,18,31-33}

This study indicates that patients with nonatopic asthma have more extensive PNS disease and more severe asthma. However, there was no correlation between sinonasal involvement on PNS-CT and asthma severity. SNSSs also did not correlate with PNS-CT findings. The patients were evaluated by two different methodologies based on CT findings, which gave us the same results. Although patients with sinonasal involvement CRSwNP and CRSsNP showed similar degrees of SNSS, PNS-CT stages and opacification scores were more increased in patients with CRSwNP.

These data suggest that SNSs commonly reported by asthmatic patients do not indicate the presence of CSD. Because SNSs are not specific to CSD, it should be remembered that some of the patients suffering from SNSs may have normal findings whereas nonsymptomatic patients may have abnormal ear, nose, and throat findings. When adults with asthma are evaluated by means of CT scanning, ~74–90% have some degree of mucosal hyperplasia, but often are asymptomatic.^{13,29,34} Therefore, diagnosis of CSD usually is based on both clinical history and physical examination and always requires sinus imaging. The primary goal of PNS-CT scan is to display an accurate image of the regional anatomy, especially the ethmoidal sinus and ostiomeatal complex. In this respect, it is important to point out that plain radiographs are of limited value in the daily practice. Therefore, chronic sinonasal involvement should be assessed using other complementary diagnostic procedures such as endoscopic examination and CT regardless of asthma severity.

Anatomic variations were detected in 77.5% of our patients. The frequency of anatomic variations varies greatly among different studies depending on the definition and assessment methods. The prevalence of anatomic variations in the literature in CSD ranges from 64.9 to 93%.^{26,27,35,36} We can speculate that high upper airway symptom scores may be attributed to these anatomic variations. Another possible explanation is that SNSs presumably reflect nasal but not sinus disease.

In earlier studies it was reported that the age of ≥ 50 years and male subjects had more severe disease on CT

scans,^{15,16} but we did not find any relationship between age, gender, and sinonasal involvement on CT scan. The presence of atopy also was emphasized as a risk factor for extensive sinonasal disease in several studies.^{12,29,30,32,37} In our study, SNSSs were similar in both atopic and nonatopic patients, whereas advanced stages on PNS-CT were found in nonatopic patients compared with atopic patients. In addition, higher TOSs on CT scan were observed in patients with nonatopic asthma.

Bresciani *et al.*¹² reported that frequency of rhinosinusitis in patients with mild-to-moderate or severe steroid-dependent asthma is similar; however, sinonasal involvement, as evaluated by clinical symptoms and CT imaging, is significantly greater in the patients with severe steroid-dependent asthma than in those with mild-to-moderate asthma. Contrary to this, Racherison *et al.*¹⁸ recently reported no correlation between CT-documented sinonasal involvement and asthma severity, parallel to our data. This suggests that severe CRS may occur even in the patients with mild asthma.

It has been shown that extensive sinonasal disease is particularly associated with adult-onset asthma, aspirin intolerance, and NP.^{12,31} Furthermore, NP was found more frequently in nonatopic subjects.³⁸ In this study, NPs were diagnosed in 31.2% of the patients and it was also found that the vast majority of patients with NPs were nonatopic and 68% of them had high scores (stage 3) on PNS-CT scans. In accordance with previous studies, it appears that NP is a predictor of extensive involvement on PNS-CT scans. As expected, they also represented more severe asthma. This is partly consistent with the study of Bresciani *et al.*¹³ in which greater ethmoidal involvement on CT scan was found in severe asthma. In another study of patients with severe asthma, extensive sinus disease on CT scans was established in 24% of the patients despite the absence of nasal symptoms.³¹ We observed no relationship between severity of sinonasal disease and asthma, although all patients with severe asthma had sinonasal involvement. This points out that CRS with/or without NP is ubiquitous in severe asthma.

This study provides further evidence of a relationship between CRS and asthma. An interesting side of this study is that upper airway symptoms did not correlate with staging on PNS-CT scan and asthma severity. This implies that the use of clinical symptoms alone is not very reliable in predicting the presence or severity of sinonasal disease, and it can not identify patients with limited or extensive sinus disease. To make an accurate diagnosis, upper airway symptoms should be supported with objective criteria such as nasal endoscopy and PNS-CT scan. Furthermore, it also should be kept in mind that extensive sinonasal

involvement may exist independently from severity of asthma.

ACKNOWLEDGMENTS

The authors thank Durdu Sertkaya (Hacettepe University, Science Faculty, Department of Statistics) for her suggestions regarding the statistical analysis.

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