Chronic sinusitis in severe asthma is related to sputum eosinophilia

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Background: Chronic rhinosinusitis and asthma are conditions that frequently coexist, particularly in severe asthma. The precise mechanism of the relationship between upper and lower airway inflammation is still a matter of debate. We hypothesized that the extent of inflammation in the nasal mucosa is related to lung function and inflammation in the bronchial mucosa in patients with severe asthma.

Objective: We sought to investigate the relationship between sinonasal inflammation as assessed on computed tomography (CT) scanning, lung function, sputum eosinophilia, and nitric oxide (NO) in exhaled air in patients with severe asthma.

Methods: Eighty-nine nonsmoking outpatients with severe asthma (29 men and 60 women; mean age 45 years; age range, 18-74 years) were included in this study. CT scans were scored (0-30) by a blinded investigator using a validated method. Lung function, NO in exhaled air, and sputum eosinophils were measured by using standard procedures.

Results: CT scans showed abnormalities in 84% of patients. Extensive sinus disease (score 12-30) was found in 24% of patients. There was a significant positive correlation between CT scores and eosinophils in peripheral blood (R_s = 0.46) and induced sputum (R_s = 0.40) and level of exhaled NO (R_s = 0.45, P < .01). CT scores were also positively related to functional residual capacity and inversely related to diffusion capacity, particularly in patients with adult-onset asthma (R_s = 0.47 and R_s = –0.53, respectively).

Conclusions: The results of this study show a direct relationship between sinonasal mucosa thickness and bronchial inflammation in severe asthma, particularly in patients with adult-onset disease. Whether sinus disease directly affects the intensity of bronchial inflammation is still an unanswered question. (J Allergy Clin Immunol 2002;109:621-6.)

Key words: *Asthma, severity-of-illness index, age of onset, inflammation, nasal mucosa, eosinophils, sputum, computed tomography, human*

Abbreviations used
CT: Computed tomography
ENT: Ear, nose, throat
FRC: Functional residual capacity
K_{CO}: Transfer coefficient expressing carbon monoxide diffusing capacity
NO: Nitric oxide

For many centuries, the coexistence of asthma and rhinosinusitis has been noted in the medical literature.[1] Up to 80% of patients with asthma have rhinitis, and over 50% of patients with sinus disease also have asthma.[2] In particular, patients with severe asthma appear to have the most prominent abnormalities on computed tomography (CT) scanning of the paranasal sinus.[3] Nasal sinus disease may contribute to poor control in asthma,[4] and sinus disease severe enough to warrant surgical intervention has been identified as an independent factor associated with frequent severe asthma exacerbations in a recent study.[5] This suggests that sinonasal involvement might be a risk factor for asthma severity and morbidity.

The interactions between the upper and lower airways are still not entirely understood, although pathophysiologic events critical to the development and clinical manifestations of these 2 diseases are similar. Indeed, many of the cells, mediators, cytokines, and neurotransmitters important in the biology of asthma and rhinosinusitis are the same.[6,7] In previous studies an association was observed between extensive sinus disease and a relative increase in the peripheral eosinophil count on the one hand[8] and a significant association between nasal mucosa eosinophilia and bronchial asthma on the other.[9] Although a causal relationship has never been proven, clinical studies indicate that proper medical and surgical management of chronic sinusitis in the asthmatic patient results in improved sinonasal and asthmatic symptoms in several patients.[10,11] Alternatively, experimentally induced sinonasal inflammation has been shown to result in worsening of bronchial hyperresponsiveness and an increase in eosinophil numbers in the lower airways.[12,13] Proposed mechanisms of this interaction include the presence of a postnasal drip of infectious or inflammatory materials, a nasal-bronchial reflex, or a systemic effect of mediators released from inflamed paranasal sinus tissue.[1]

Therefore we hypothesized that the extent of inflammation in the sinonasal mucosa is directly related to lung func-

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tion and inflammation in the bronchial mucosa in patients with severe asthma. To that end, we investigated, in these patients, the relationship between sinonasal involvement as assessed on CT scanning on the one hand and various lung function parameters, sputum eosinophilia, and levels of nitric oxide (NO) in exhaled air on the other.

METHODS

Patients

Eighty-nine patients with severe bronchial asthma[14] (age range, 18-74 years) were recruited from the outpatient pulmonary departments of 10 hospitals in the western part of The Netherlands. The patients had a history of episodic dyspnea and wheezing, a documented (recently or in the past) reversibility in FEV_1 of greater than 12% of predicted value,[15] or hyperresponsiveness to inhaled histamine (PC_{20} of <8 mg/mL).[16] They were treated with high doses of inhaled corticosteroids (≥1600 μg/d beclomethasone or equivalent) and long- and short-acting bronchodilators for more than 1 year and were all nonsmokers (smoking history of ≤10 pack-years). Thirty-three (37%) of the patients used nasal corticosteroids. All patients were symptomatic and had at least one severe exacerbation during the past year requiring a course of oral corticosteroids or were on maintenance therapy with oral prednisone. The study was approved by the hospital medical ethics committees, and all patients gave informed consent.

Design

This study was undertaken as part of a larger study on mechanisms of severe asthma performed in our department.[5] At entry, patient and disease characteristics were documented according to a detailed structured questionnaire. The age at onset of asthma was judged as accurately as possible and used to calculate the duration of asthma. In case of uncertainty, the earliest respiratory symptoms were taken into account. Then a blood sample was taken, and lung function measurements were performed. On a separate day, nasal symptoms were assessed; nasal endoscopy was carried out by an ear, nose, and throat specialist; and standardized CT scanning of the paranasal sinus was performed.[8]

Pulmonary function tests were performed at least 12 hours after discontinuation of long-acting β_2-agonists (if possible). First, slow inspiratory vital capacity was measured, followed by FEV_1.[15] Functional residual capacity (FRC) and total lung capacity were measured by using the multibreath helium equilibration method,[15] and the transfer coefficient expressing carbon monoxide diffusing capacity (K_{CO}) was measured by using the single-breath method.[17] All lung function parameters were expressed as percentages of predicted values.[15] Airway responsiveness to histamine (expressed as PC_{20} histamine)[16] was measured by using standardized procedures. Exhaled NO levels from the lower airways were measured according to a validated technique described in detail elsewhere.[18] With this technique, subjects performed a slow vital capacity maneuver and expired with a constant expiratory flow against an expiratory resistance of 5 cm H_2O to prevent bias of the measurement with nasal NO.

Atopic status was assessed by means of IgE immunoassay (UniCAP; Pharmacia and Upjohn, Uppsala, Sweden). Eosinophils in blood were measured with a standard automated cell counter.

Sputum was induced and processed according to a standardized protocol,[19] with some modifications for safety reasons.[20] In short, saline solutions were inhaled 3 times for 5 minutes each, with frequent monitoring of the FEV_1. Depending on baseline FEV_1, the induced fall in FEV_1, and the accompanying symptoms, isotonic saline solution only or increasing saline solution concentrations of 0.9%, 3.0%, and 4.5% were used.

Nasal endoscopy and CT scanning of the nasal sinus

Nasal endoscopy was used to assess deformations comprising the middle meatus, septal deformation, purulent secretions, and polyps. Limited coronal sinus CT scanning was performed. Scans were analyzed for evidence of mucosa thickening in the sinuses, osteomeatal complexes, and nasal cavities.[21] A CT-scan score was assigned, as previously described by Newman et al.[8] A total of 30 points were allowed (21 from the sinus, 6 from the osteomeatal complexes, and 3 from the nasal passages). The total CT-scan score was used to classify the patients as having limited disease (CT score of 0-11) or extensive disease (CT score of ≥12). The sinus CT scans were reviewed by one of the authors (F.T.B.), an observer experienced in interpreting sinus CT scans who was blinded regarding the patients' history and examinations.

Statistical analysis

Nonnormally distributed parameters were log transformed before statistical analysis. PC_{20} histamine was censored to 8.0 mg/mL if a fall in FEV_1 of 20% or greater was not reached at the highest dose given (8 mg/mL). Differences between patients with and without extensive sinus disease were analyzed by using unpaired Student *t* tests, χ^2 analyses, and nonparametric tests, where appropriate.[22] Spearman rank correlation coefficients were used to analyze the relationship between CT scores and inflammatory and lung-function parameters. All analyses were performed with the Statistical Package of the Social Sciences (SPSS 10.0). A *P* value of less than .05 was considered statistically significant.

RESULTS

Patient characteristics

In the whole group of 89 patients with severe asthma, the median CT-scan score was 5.0 (range, 0-29). According to the cut-off level, 21 (23.6%; 95% CI, 15%-33%) of the 89 patients had extensive paranasal sinus disease, with a median CT-scan score of 19.0 (range, 12-29), whereas 68 (76.4%) patients were classified as having limited sinus disease, with a median score of 3.0 (range, 0-11).

When comparing both groups, patients with extensive sinus disease were significantly older and had a shorter asthma duration (Table I). In addition, the age at onset of asthma was higher in this group of patients. They more frequently used nasal corticosteroids and relatively more frequently reported being sensitive to aspirin or nonsteroidal anti-inflammatory drugs (4/5 patients vs 6/19 patients of a total of 24 patients who reported to have used aspirin in the past). There was no difference between the groups in daily dose of oral or inhaled corticosteroid ($P > .3$), nor was there a difference in atopic status. Although only a limited smoking history was allowed, the patients with CT abnormalities tended to have an increased cigarette exposure in the past compared with those without such abnormalities.

Nasal symptoms and nasal endoscopy

Patients with and without extensive sinus disease could not be distinguished on the basis of nasal symptoms ($P > .2$, Fig 1). Remarkably, 30% of the patients without any symptoms of nasal congestion, olfactory disturbance, headache, or facial pain had extensive sinus disease, with

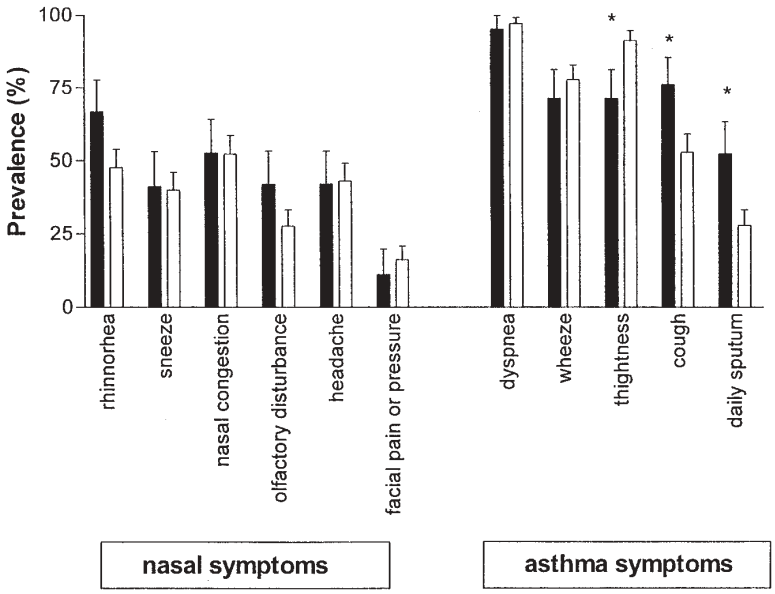

FIG 1. Prevalence of nasal symptoms *(left)* and asthma symptoms *(right)* in severely asthmatic patients with extensive sinus disease *(filled bars)* versus those without sinus disease *(open bars). Error bars* represent SEM (*$P < .05$).

TABLE I. Characteristics of patients with severe asthma with and without extensive sinus disease

	Extensive sinus disease (n = 21)	Limited sinus disease (n = 68)	*P* value
Age (y)*	50.4 ± 14.8	42.7 ± 13.1	.02
Female sex (%)	61.9	69.1	.54
Age at onset of asthma (y)†	35.0 (1.0-63)	11.5 (0.5-68)	<.001
Asthma duration (y)†	12.0 (2-43)	23 (2-63)	.01
Maintenance oral steroids (%)	38.1	26.9	.33
Nasal corticosteroids (%)	57.1	30.9	.03
Dose ICS (μg/d)†	1600 (1600-3600)	1600 (1600-6400)	.50
Smoking history (pack-years)†	1 (0-10)	0 (0-10)	.09
History aspirin/NSAID sensitivity	4/5	6/19	.05
Positive atopic status (%)	47.6	63.2	.20

ICS, Inhaled corticosteroids, beclomethasone equivalent; *NSAID*, nonsteroidal anti-inflammatory drug.
*Mean ± SD
†Median (range).
‡Only 24 patients were reported to have used these medications.

CT-scan scores of up to 24. As might be expected, nasal endoscopy findings did differ between the groups. Signs of postnasal drip and nasal secretion were observed in 16.7% and 31.6% of patients with extensive sinus disease, respectively, whereas these signs were present in only 1.6% and 10.8% of the control group, respectively ($P <$ .05). In addition, 35.0% of the patients with a CT-scan score of 12 or greater appeared to have nasal polyps compared with 6.3% of the patients without extensive sinus disease ($P = .001$). Finally, deformation of the middle meatus was observed in a majority (65.0%) of the patients with extensive sinus disease and only in 32.9% of the patients with limited disease ($P = .01$).

Asthma symptoms and asthma morbidity

Patients with extensive sinus disease less frequently reported symptoms of chest tightness compared with the control group (71.4% vs 91.2%, $P = .02$), whereas cough and daily sputum production were more prevalent in the former group (76.2% vs 52.9%, $P = .05$; 52.4% vs 27.9%, $P = .04$, respectively; Fig 1). The level of asthma control as measured by exercise tolerance, nocturnal symptoms, and use of rescue medication was not different between the groups ($P > .5$), nor was there a difference in the number of exacerbations, emergency visits, or hospitalizations in the last year ($P > .5$).

Physiologic and inflammatory parameters

There was no difference in FEV_1/slow inspiratory vital capacity, total lung capacity, and PC_{20} histamine between the groups (Table II). The level of FRC percent predicted was increased in the patients with extensive sinus disease, whereas diffusing capacity (K_{CO} percent predicted) was significantly decreased compared with that seen in the patients with limited disease. With respect to inflammatory characteristics, patients with extensive sinus dis-

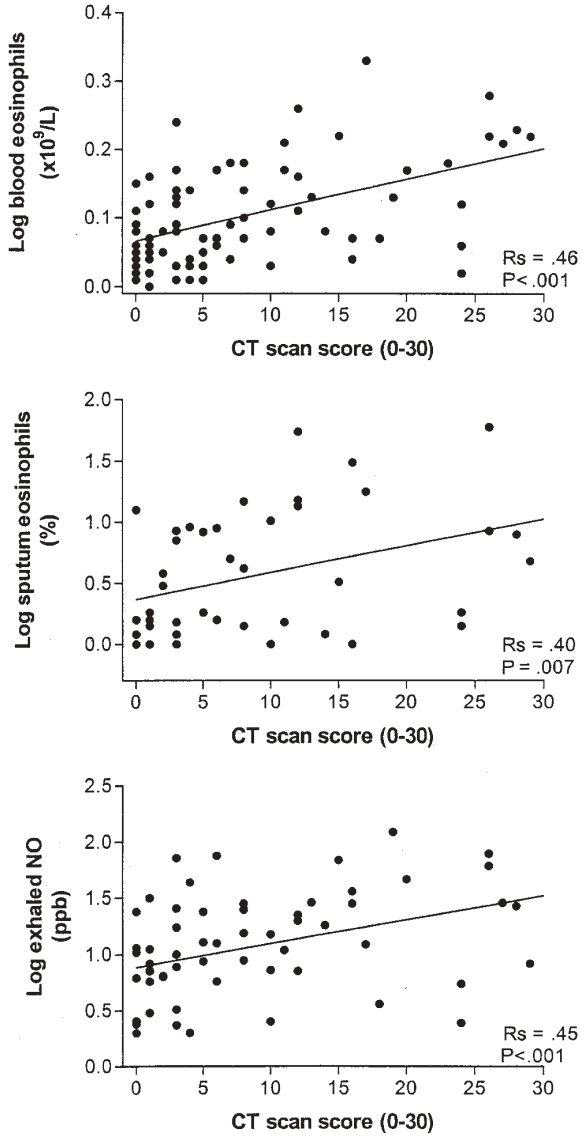

FIG 2. Relationship between sinus CT-scan score and level of eosinophils in peripheral blood *(upper panel)*, eosinophils in induced sputum *(middle panel)*, and NO in exhaled air *(lower panel)* in patients with severe asthma.

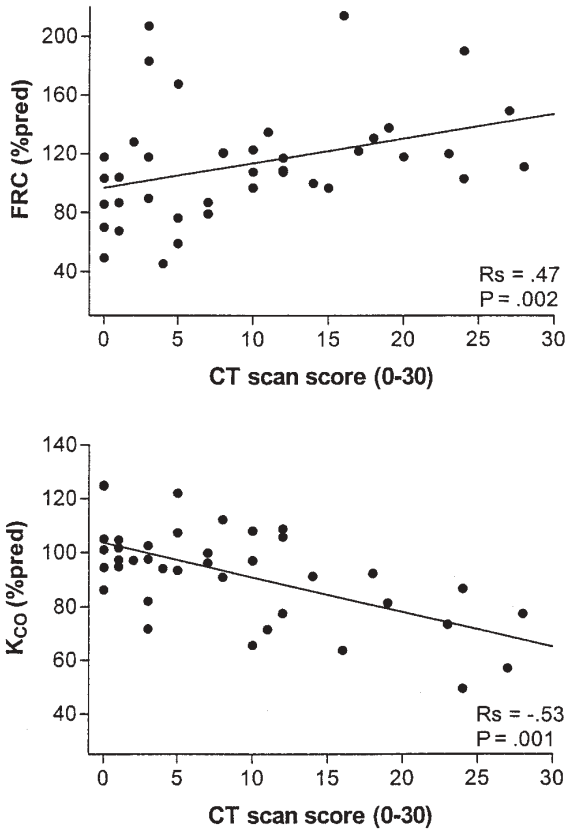

FIG 3. Relationship between sinus CT-scan score and level of FRC *(upper panel)* and K_{CO} *(lower panel)* in patients with adult-onset severe asthma.

ease showed a highly significant increase in levels of eosinophils, both in peripheral blood and induced sputum, and in exhaled NO compared with those in the control group ($P < .01$).

The correlation analysis showed that eosinophil numbers in peripheral blood and eosinophil percentages in induced sputum were significantly correlated with CT-scan scores, as were the levels of NO in exhaled air (Fig 2). Furthermore, the extent of sinus disease was positively related to the level of FRC and inversely to K_{CO}, particularly in patients with adult-onset asthma (Fig 3).

DISCUSSION

The present study shows that sinus CT-scan abnormalities are present in the vast majority of patients with severe asthma, even in the absence of nasal symptoms. The extent of sinus disease (as measured on CT scanning) is positively related to airway inflammation, as reflected by eosinophils in the lower airways and the systemic circulation, as well as the level of NO in exhaled air. Patients with extensive sinus disease more frequently have adult-onset asthma, and in these patients mucosa thickening on CT scanning is associated with air trapping and decreased K_{CO}. The results are indicative of an association between sinonasal and lower airways inflammation in patients with severe asthma. This suggests that the observed improvement in asthma control after treatment of chronic sinusitis could be the result of reduced bronchial inflammation.

The present findings confirm and extend earlier studies showing a close relationship between upper and lower airways diseases. As early as the second century AD, the coexistence of sinus disease and asthma was noted by Galen,[23] and many studies on this relationship have been published ever since. Newman et al[8] showed an association between extensive sinus disease on CT scanning with a relative increase in the peripheral eosinophil count. Recently, Bresciani et al[3] have shown that chronic sinus disease is a major problem in patients with severe asthma and that the extent of the abnormalities on CT scanning of the paranasal sinuses is related to the

TABLE II. Comparison of physiologic and inflammatory parameters in patients with severe asthma with and without extensive sinus disease

	Extensive sinus disease (n = 21)	Limited sinus disease (n = 68)	*P* value
Baseline FEV_1/VC (% predicted)*	70.2 ± 20.9	75.4 ± 21.5	.33
TLC (% predicted)*	102.8 ± 15.7	97.5 ± 15.2	.19
FRC (% predicted)*	132.1 ± 34.6	111.8 ± 33.9	.03
K_{CO} (% predicted)*	80.9 ± 18.4	94.3 ± 15.6	.006
PC_{20} histamine (mg/mL)†	1.09 ± 2.4	0.79 ± 2.8	.63
Exhaled NO (ppb)‡	27.1 (2-124)	8.5 (2-76)	.002
Blood eosinophils (10^9/L)‡	0.44 (0.05-1.12)	0.17 (0.01-1.29)	<.001
Sputum eosinophils (%)‡	7.3 (0-59)	0.7 (0-14)	.007

VC, Slow inspiratory vital capacity; *TLC*, total lung capacity.
*Mean ± SD.
†Geometric mean ± SD (in doubling doses).
‡Median (range).

number of eosinophils in peripheral blood. Harlin et al[9] found a significant association between tissue eosinophilia and asthma in adults with chronic sinusitis. Other studies showed a significant relationship between eosinophil cell counts in the nose and in the lower airways in mild asthma,[7,24] supporting the hypothesis that asthma and rhinosinusitis are clinical expressions of the same disease entity. Our findings in patients with severe asthma extend these observations by showing a close relationship between high scores on sinus CT scans and increased percentages of eosinophils in induced sputum and elevated levels of NO in exhaled air. This suggests that these concurrent inflammatory processes are driven by similar pathogenic mechanisms.

We do not think that the results of our study are biased by patient selection or methodological errors. The patients were well defined and considered to represent the population of patients with severe asthma who regularly visit chest physicians in general hospitals. The extent of sinus disease was assessed by an independent observer, using a validated system for quantification.[8] Although data on sputum samples were not available in all patients because of low prebronchodilator FEV_1 or patient inability to produce sputum, we do not think that this has significantly influenced the results because there were no differences between the patients who were able or unable to produce adequate sputum samples with respect to CT-scan scores (data not shown).

The relationship between sinus disease, eosinophils in peripheral blood, and lower airways inflammation suggests that asthma is not just a local disorder of the airways but truly a systemic disease. The observations that sputum eosinophilia is an independent predictor of poor lung function in severe asthma[25] and that pulmonary function can improve after surgical or pharmacologic treatment of chronic sinusitis or nasal polyposis[10] suggest a causal relationship as well. It might be hypothesized that inflamed sinus tissue not only releases mediators and cytokines into the circulation, thereby directly inducing inflammation of the lower airways, but also releases chemotactic factors that recruit eosinophils from the bone marrow and from the circulation into the upper and lower airways.[26] Indeed, there is recent evidence of expression of eotaxin mRNA in the sinonasal mucosa of patients with chronic sinusitis,[27] as well as in the bronchial mucosa of asthmatic subjects.[28] This raises the possibility that the observed improvement of asthmatic disease after treatment of chronic sinusitis[1,11] could be the result of reduced sinonasal, as well as bronchial, inflammation. However, our finding that clinical markers of asthma control, such as nocturnal symptoms, exacerbations, and emergency visits, were not different between patients with or without extensive sinus disease suggests that factors other than sinonasal inflammation also contribute to loss of control and development of asthma exacerbations.

An important observation of the present study is that there was no difference in the prevalence of nasal congestion, olfactory disturbance, headache, facial pain, or pressure between subjects with or without extensive sinus disease. This suggests that our traditional sinus-symptom scoring system is not very accurate in predicting either the presence of actual sinus disease or its severity. Presumably this shows that our symptoms scores reflect nasal, and not sinus, disease. It implies that for an accurate estimation of the presence and severity of sinus disease, nasendoscopy and CT scanning of the sinuses are more or less obligatory diagnostic procedures.

In our study extensive sinus disease appeared to be associated with adult-onset asthma, aspirin sensitivity, and nasal polyps, a well-recognized clinical entity associated with higher morbidity and poor outcome of asthma.[29] It has been suggested that this type of asthma might have a different cause, but its precise pathophysiologic mechanism remains obscure. Our finding of an association among sinus disease, air trapping, and impaired diffusion capacity in patients with adult-onset asthma suggests that mechanisms other than bronchoconstriction and mucosa inflammation of the larger airways are also involved. A likely explanation might be that peripheral airways and lung parenchyma additionally take part in the disease process, as has been shown recently.[30,31] A reduced diffusion capacity in the patients with severe asthma might be caused by an extension of the inflammatory infiltrate into the alveolar wall, as has been observed in fatal asthma,[32] or, alternatively, by the

presence of "pseudoemphysema," as has been described recently by Gelb and Zamel.[33]

The present findings may have implications for the management of patients with severe asthma, particularly those with adult-onset asthma. It appears that even in the absence of significant nasal complaints these patients should undergo ear, nose, and throat evaluation, including CT scanning, to assess the extent of sinus disease. In case of significant abnormalities, treatment with nasal corticosteroids or even sinonasal surgery should be considered. Moreover, peripheral airways involvement, as well as sinus disease, suggests ongoing inflammation in regions of the airways that are not or are hardly accessible to inhaled corticosteroids. This implies that in these patients treatment with systemic anti-inflammatory drugs might be indicated in addition to maximal doses of inhaled medication.

In summary, the present study provides evidence of a direct relationship between chronic rhinosinusitis and lower airway inflammation in severe asthma, particularly in those with adult-onset disease. Also, peripheral airways seem to be involved in these patients, which might have important consequences for prognosis and treatment.

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