

Rhinosinusitis in severe asthma

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Background: Chronic rhinosinusitis is a common comorbidity of asthma. However, sinonasal involvement in severe steroid-dependent asthma is still undefined.

Objective: The aim of the study was to evaluate chronic rhinosinusitis in 35 patients with severe steroid-dependent asthma by using a clinical score and coronal computed tomography (CT) scanning.

Methods: Thirty-five subjects (16 female subjects) with severe asthma requiring daily doses of oral corticosteroids were compared with 34 patients (19 female patients) with mild-to-moderate asthma. Sinonasal involvement was studied by using clinical and CT scores. Airflow obstruction, therapy requirement, and asthma triggering factors were carefully assessed.

Results: The proportion of patients with symptoms of rhinosinusitis was similar in both groups of asthmatic subjects (74% in patients with severe steroid-dependent asthma and 70% in patients with mild-to-moderate asthma). All subjects with steroid-dependent asthma versus 88% of subjects with mild-to-moderate asthma had abnormal CT scan results. The clinical ($P < .05$) and CT scan ($P < .0005$) severity scores were higher in the subjects with severe steroid-dependent asthma. In both groups the CT scan scores were correlated to the clinical scores ($P < .0001$ and $P < .006$), but only in the mild-to-moderate group were both scores correlated with high significance ($P < .002$ and $P < .0005$) to the absolute number of blood eosinophils.

Conclusion: 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 scan imaging, is significantly greater in the patients with severe steroid-dependent asthma than in those with mild-to-moderate asthma. (*J Allergy Clin Immunol* 2001;107:73-80.)

Key words: Chronic rhinosinusitis, computed tomography, severe asthma, eosinophils, oral corticosteroids

Chronic rhinosinusitis is a common comorbidity of asthma. It is clinically defined by the persistence of upper respiratory signs and symptoms (nasal congestion or obstruction, nasal discharge, headache, facial pain or pressure, or olfactory disturbance) for more than 12 weeks after failure of appropriate medical treatment.^{1,2}

Abbreviations used

CT: Computed tomography
OMC: Ostiomeatal complex

Currently, computed tomography (CT) is the imaging technique of choice for the study of the nose and paranasal sinuses,³ particularly for the ethmoid and sphenoid sinuses.^{4,5} Coronal CT imaging perpendicular to the bony palate affords the best display of the ostiomeatal complex (OMC) because it resembles the endoscopic view most closely.⁶ Evaluation of OMC is of importance because rhinosinusitis is considered secondary to ostiomeatal obstruction with impairment of sinus ventilation and mucociliary clearance.⁷⁻⁹

Association of asthma with rhinosinusitis has been known and described in the medical literature for more than 70 years.¹⁰ However, whether rhinosinusitis is a precipitating factor for bronchial asthma is still debated.¹¹ Presently, rhinosinusitis and asthma are believed to be inflammatory processes in which eosinophils and the airway epithelium play a central role: eosinophils are thought to damage the epithelium by releasing cytokines and other proinflammatory proteins, and the damaged epithelium would react, releasing cytokines and chemokines that further attract eosinophils, thus starting a vicious circle of actions and reactions that activates and sustains inflammation. Environmental irritants or infection alone may initiate this process or enhance the action of allergens.¹² Association of chronic rhinosinusitis with asthma and allergy appears to be restricted to the asthmatic population with extensive sinonasal disease¹³; furthermore, peripheral eosinophilia in patients with rhinosinusitis is a high likelihood marker of extensive disease.¹⁴

The natural history of asthma is still poorly characterized; however, we know that a small proportion of asthmatic patients have a most severe form that requires, despite new and improved inhalation therapies, a continuous and long-term treatment with oral corticosteroids to control symptoms.¹⁵⁻¹⁷

The extent of sinonasal involvement in patients with severe steroid-dependent asthma is still unknown.

The aim of this study was to evaluate sinonasal involvement in these patients and to assess the relationships between chronic rhinosinusitis and asthma severity, corticosteroid requirement, peripheral eosinophilia, and allergy to common aeroallergens. A cross-sectional case-control study design was used: 35 patients with severe steroid-dependent asthma were compared with 34

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patients with mild-to-moderate persistent asthma, the severity of which was graded according to GINA (Global Initiative for Asthma) guidelines.¹⁸ In all patients, rhinosinusitis was assessed by using a clinical score and coronal CT scanning.

METHODS

Patients

Sixty-nine adult asthmatic subjects were recruited from the outpatient clinic of the Service des Maladies Respiratoire in the University Hospital (CHU) of Montpellier, France. All patients fulfilled the international guidelines for asthma diagnosis,^{19,20} had typical clinical symptoms, had documented airways reversibility ($>20\%$ improvement in FEV₁ after 200 μ g of salbutamol), and had increased airway responsiveness to methacholine (PC₂₀ <8 mg with FEV₁ $>70\%$ of predicted values). Pulmonary function tests (spirometry) were carried out on each patient by using the same equipment (Pneumoscreen; E. Jaeger Laboratories, Wurzburg, Germany). Baseline pulmonary function measurements were made according to the American Thoracic Society reference values.²¹ Methacholine inhalation challenges were performed by using standard procedures.²² Control of the disease was assessed by measuring the peak expiratory flow rate and nocturnal asthma symptoms.¹⁷ None of the patients were current smokers, and none had smoked within the previous 2 years. No patient had any bronchial or respiratory tract infection during the month preceding the study. All patients had been followed in the university hospital outpatient clinic, at least within the previous year. Previous nasal surgery was an exclusion criteria. Aspirin intolerance was diagnosed by a relevant clinical history and a positive oral provocation test response according to the technique of Stevenson.²³ Allergy was based on the presence of at least one positive skin prick test response (Stallergènes, Anthony, France) to common allergens of the Montpellier area, the measurement of allergen-specific serum IgE, or both (Pharmacia CAP System; Pharmacia-Upjohn, Uppsala, Sweden). All investigations were performed out of the pollen season. Peripheral blood eosinophils were counted by means of a Technicon Hemalog (Technicon, Tarrytown, NY), and blood samples were taken the same day CT scans were performed. Severity of asthma was defined according to the GINA guidelines.¹⁸

Thirty-five subjects were defined as having severe asthma (range, 20-70 years; median, 57 years; 16 women; Table I), and they are described as steroid dependent because we failed to wean them from oral corticosteroid intake despite the optimal treatment and management. All patients required a long-term continuous daily treatment with inhaled corticosteroids (1500-2000 μ g beclomethasone dipropionate equivalent), long-acting inhaled β_2 -agonists (formoterol), and oral corticosteroids (median dose, 20 mg of prednisone equivalent) to control the disease symptoms. In all patients asthma symptoms started before 45 years of age. Asthma duration ranged from 2 to 40 years (median duration, 14 years). Compliance to oral corticosteroid treatment in the group with severe steroid-dependent asthma was checked by evaluation of 8 AM serum cortisol levels, and bone mineral density was assessed by using absorptiometry. All patients included in the present study had low serum cortisol levels and abnormal T scores in the lumbar spine and proximal femur. These findings suggested a short- and long-term compliance to the oral corticosteroid prescription; however, there is no single way to precisely assess long-term compliance in chronic diseases, such as severe asthma.

Thirty-four asthmatic subjects were defined as having mild persistent and moderate persistent disease (range, 19-75 years; median, 48 years; 19 women; Table I), 45% of which were receiving inhaled corticosteroids (500-1000 μ g beclomethasone dipropionate equivalent), as prescribed by the GINA guidelines.¹⁸

Asthma duration ranged from 6 to 35 years (median duration, 16 years). No patient had received oral corticosteroids within the past 3 months.

The study was approved by the Ethics Committee of the University, and the patients gave informed consent.

Clinical evaluation of rhinosinusitis

Acute rhinosinusitis, defined by the presence of sinonasal symptoms for a period of less than 12 weeks, was an exclusion criteria when present in the 6 months preceding this study.

Chronic rhinosinusitis was clinically defined by the presence of persistent symptoms and signs (nasal congestion or obstruction, nasal discharge, headache, facial pain or pressure, or olfactory disturbance) for at least 12 weeks after failure of appropriate medical treatment.² Such treatment consisting of at least 14 days of a broad-spectrum oral antibiotic (amoxicillin/potassium clavulanate or sulfamethoxazole-trimethoprim). In patients with a history of severe sinonasal symptoms a topical steroid, oral antihistamine, or both was added to the treatment. Subjective assessment of rhinosinusitis symptoms out of the specific pollen season was done by the patients with the use of a visual analog scale rating symptoms from 0 (none) to 10 (most severe). This method of rating was previously validated.¹⁻²⁴ The following symptoms were scored on 6 different scales: facial pain or pressure; headache; nasal blockage or congestion; nasal discharge; olfactory disturbance; and total symptoms. A total of 60 points was allowed.

Sinus CT scan

Limited coronal sinus CT scanning was performed on all subjects during the 14 days after the interruption of a second cycle of antibiotic treatment. A CT ProSpeed was used (General Electric Medical System, Milwaukee, Wis). Scans were analyzed for evidence of mucosal thickening in the sinuses, OMCs, and nasal cavities.²⁵ A CT scan score was assigned, as previously described by Hoover et al (Table II).¹³ A total of 30 points was allowed (21 from the sinus, 6 from the OMCs, and 3 from the nasal passages). The total CT scan score was used to classify the patients as having limited disease (CT score, 0-11) or extensive disease (CT score, >12). The sinus CT scans were initially reviewed by one of the authors (H.V.), an observer experienced in interpreting sinus CT scans who was blinded regarding the patients' history and examinations. Blind reading of the CT scans by a second investigator (L.P.) showed a close correlation with the previous reading ($\kappa = 0.95$, interobserver agreement).

Statistical analysis

The data regarding the 2 groups of patients were compared by using the nonparametric Mann-Whitney *U* test. The correlation analysis was accomplished by using the Spearman rank test. The frequency analysis of symptom score and CT scan score distribution were obtained by using the χ^2 test. Results are expressed as medians and 25th-75th percentiles.

RESULTS

Rhinosinusitis symptoms

In the patients with severe steroid-dependent asthma, 74% reported persistent nasal symptoms compared with 70% of the patients with mild-to-moderate asthma (Table III). However, the total symptom score was significantly higher in patients with severe steroid-dependent asthma compared with those with mild-to-moderate asthma ($P < .05$, Mann-Whitney *U* test; Fig 1); moreover, 58% of the patients with severe steroid-dependent asthma reported an extensive disease (clinical score over 20 points) com-

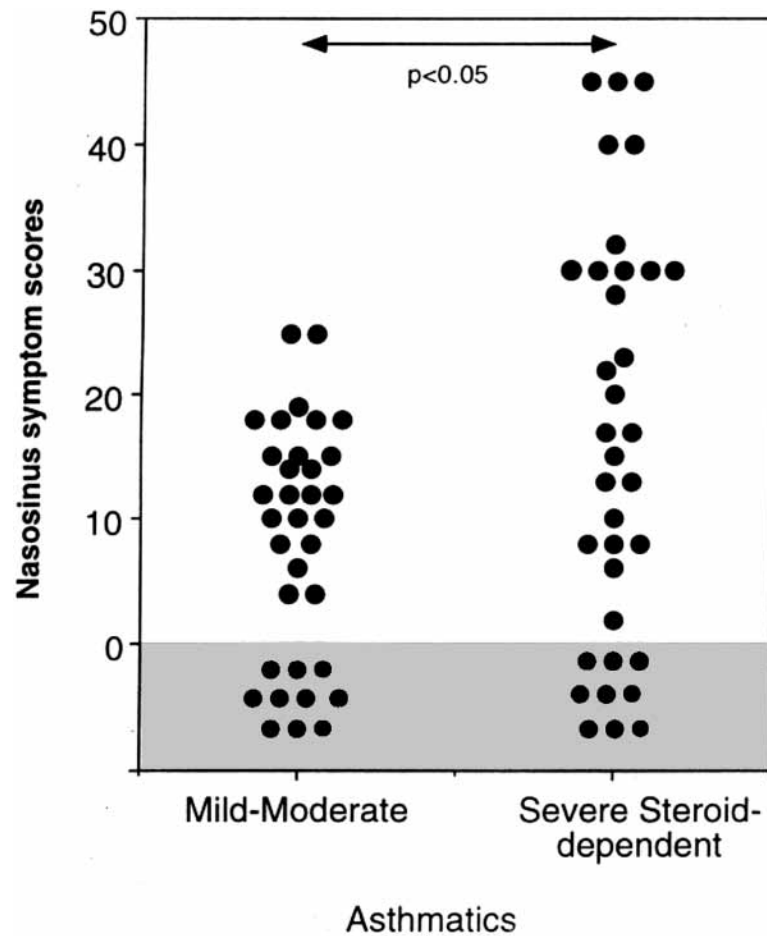


FIG 1. Sinonasal symptom total scores in the patients with mild-to-moderate and severe steroid-dependent asthma.

TABLE I. Demographic characteristics of the asthmatic subjects

	Mild-to-moderate asthma	Severe steroid-dependent asthma
No. of subjects	34	35
Sex (F)	19	16
Age (y)	48 (30-59)	57 (45-63)
Duration of asthma (y)	16 (10-30)	14 (6-38)
Asthma severity (% patients)		
Mild	59	0
Moderate persistent	41	0
Severe	0	100
Inhaled corticosteroids		
Patients (%)	45	100
Daily dose (μg)*	500-1000	1500-2000
Oral corticotherapy		
Duration (y)	0	3 (2-13)
Daily dose ($\text{mg}^\dagger$)	0	20 (15-38)
Allergy (%)	58	48
Aspirin intolerance, n (%)	1 (3)	4 (11)
Blood eosinophils ($/\text{mm}^3$)	397 (200-469)	296 (150-536)
FEV ₁ (% predicted)	85 (67-100)	70 (53-78)*

Results are expressed as medians and 25th-75th percentiles. Values in parentheses are ranges.

*Equivalent beclomethasone dipropionate.

† Equivalent prednisone.

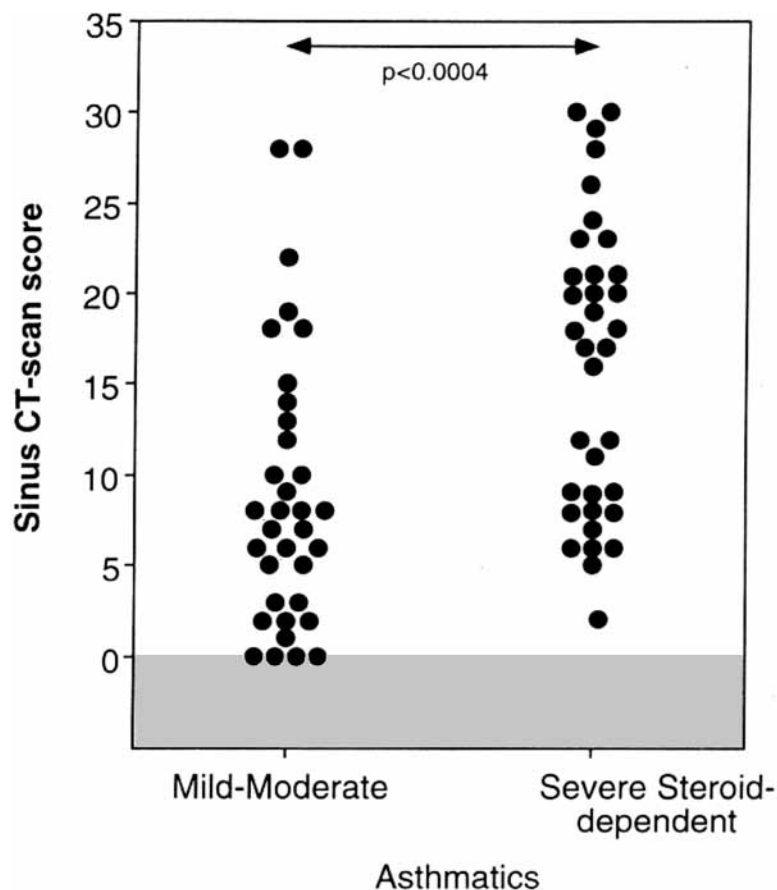


FIG 2. Sinus CT scan total scores in the patients with mild-to-moderate and severe steroid-dependent asthma.

TABLE II. Sinus CT scan score

Nasal passages	3	(0-3)		
OMC	6	(0-3 each)		
Sinuses	21 points			
Points for mucosal thickening	0	1	2	3
Frontal (2)	0-1 mm	2-5 mm	6-9 mm	>10 mm
Maxillary (2)	0-1 mm	2-5 mm	6-9 mm	>10 mm
Sphenoid (1)	0-1 mm	2-5 mm	6-9 mm	>10 mm
Ethmoid (2)	0 mm	1 mm	2-3 mm	>4 mm

Maximal score is 30 points.

pared with only 8.6% of patients with mild-to-moderate disease ($P = .001$, χ^2 test). No patient with mild-to-moderate asthma manifested olfactory disturbances, facial pain or pressure, and headaches.

Sinus CT scan

All patients with severe steroid-dependent asthma and 88% of the patients with mild-to-moderate asthma had sinus CT scan abnormalities (Table IV). The sinus CT scan score was, however, significantly higher in the group with severe disease ($P < .0004$, Mann-Whitney U test; Fig 2). Twenty (58%) of the patients with steroid-dependent asthma and 10 (30%) of the patients with mild-to-moderate asthma had extensive sinus involve-

ment (score >12 ; $P = .028$, χ^2 test). Among the different sinus abnormalities, the major difference between the 2 groups of asthmatic patients was the significantly higher frequency ($P < .001$, Mann-Whitney U test) of ethmoidal involvement in the group with severe steroid-dependent disease (97% in patients with severe asthma vs 61% in patients with mild-to-moderate asthma).

Correlations between results

A significant correlation was found between the clinical score and the sinus CT scan score in both the group with severe steroid-dependent asthma ($\rho = 0.8$ and $P < .0001$, Spearman rank test) and the group with mild-to-moderate asthma ($\rho = 0.47$ and $P < .006$, Spearman rank test; Fig 3).

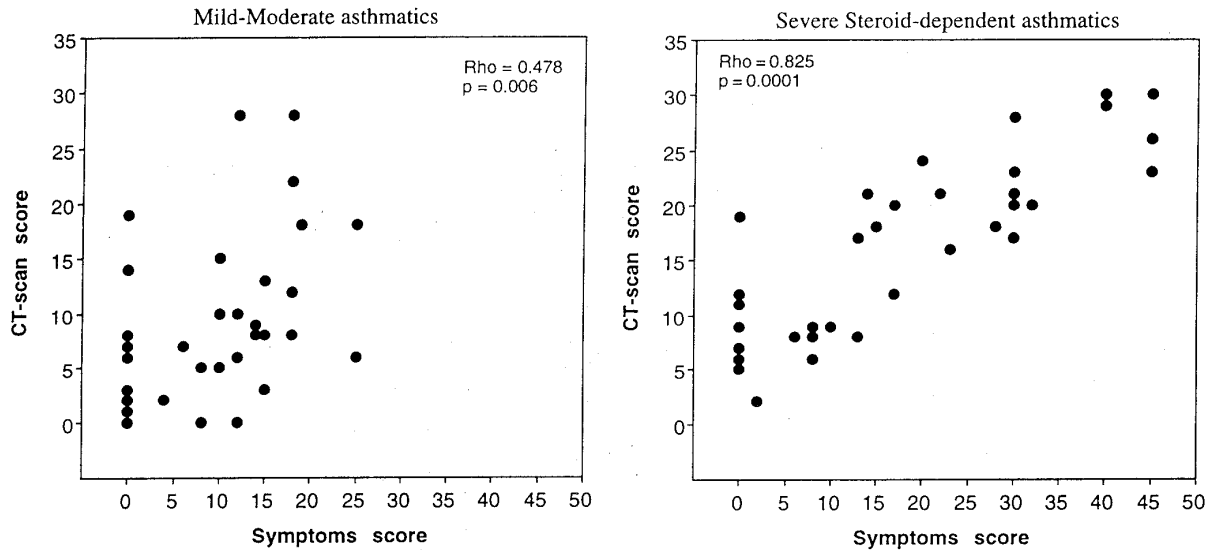


FIG 3. Correlation between the sinonasal symptom total scores and the sinus CT scan scores in the patients with mild-to-moderate and severe steroid-dependent asthma.

TABLE III. Rhinosinusitis symptoms and symptom scores

	Mild-to-moderate asthma (n = 34)	Severe steroid-dependent asthma (n = 35)
Symptomatic patients (% of total)	70	74
Nasal congestion*	75	92
Nasal discharge*	62.5	69.2
Facial pain or pressure*	0	4
Headache*	0	4
Olfactory disturbance*	0	19
Total symptom score†	10 (0-15)	15 (3-30)
Total score >20‡	8.6	58

*Percentage of symptomatic patients.

†Results as medians and 25th-75th percentiles ($P < .05$).

‡ $P = .001$.

Peripheral blood eosinophilic counts were significantly correlated at a high degree with both the sinonasal clinical scores ($\rho = 0.6$ and $P < .0005$, Spearman rank test) and the sinus CT scan scores ($\rho = 0.56$ and $P < .002$, Spearman rank test) only in the group of patients with mild-to-moderate asthma (Fig 4).

Airflow obstruction (FEV_1) or exacerbation rates during the previous year, age, sex, asthma duration, corticosteroid intake duration, or doses were all found not to be related to any clinical or CT scan sinonasal parameter. Precipitating factors, such as allergy or aspirin intolerance, were also not found to be related to any sinonasal parameter.

The analysis of both the clinical and CT scan characteristics in the steroid-dependent group did not lead to any distinguishing figure, and thus it was not possible to subdivide these patients. The only observed evidence is the presence of anosmia in the patients with severe steroid-dependent asthma with symptom scores between 35 and 50, as logically expected, and this symptom was not correlated with aspirin intolerance.

DISCUSSION

Chronic rhinosinusitis has been known for a long time to be associated with asthma, both in children and adults.¹⁰ Accordingly, this study showed that a high prevalence of sinus disease exists in asthmatic subjects and that a similar prevalence was found in both the populations taken in examination. This prevalence supports the increasing evidence of a close relation between upper and lower airway diseases, although this study was not designed to offer understandings about the pathophysiologic interdependence mechanisms, for which further studies are highly welcome. Moreover, the highly significant correlation found between symptom scores and CT scan scores in both patients with mild-to-moderate and severe asthma is a finding that further supports the validity of our CT scan results. Furthermore, we find a previously unknown definite correlation between severity of asthma and the clinical and imaging features of rhinosinusitis. This finding is in contrast with a previous study²⁶ showing no correlation between severity of asthma and

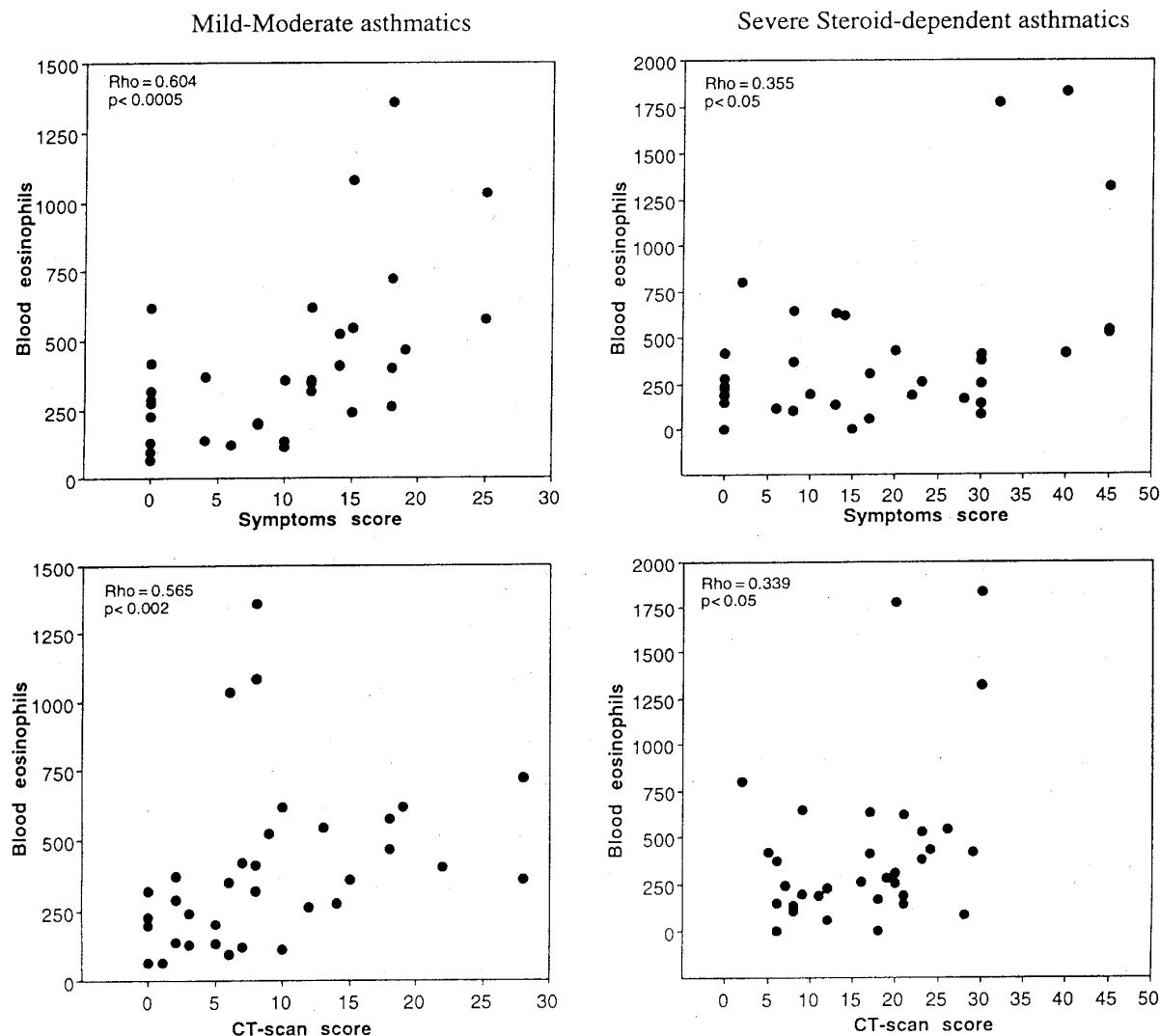


FIG 4. Correlation between the sinonasal symptoms total scores, the sinus CT scan scores, and the peripheral blood total eosinophil counts in the patients with mild-to-moderate and severe steroid-dependent asthma.

TABLE IV. Sinus CT scan abnormalities and CT scan scores

	Mild-to-moderate asthma (n = 34)	Severe steroid-dependent asthma (n = 35)
Abnormal CT scans (% of total patients)	88	100
Nasal passages*	75	100
OMC*	93	100
Sinus involvement*		
Ethmoid†	61	97
Frontal	28	45
Maxillary	82	90
Sphenoid	36	55
Total CT scan score‡	7 (3-13)	17 (8-21)
Score >12*§	30	58

*Percentage of patients with abnormal CT scans.

†P < .001.

‡Results as medians and 25th-75th percentiles (P < .004).

§P = .03.

morphologic abnormalities of the upper airways. The lack of correlation found in this previous study may be explained by the use of x-ray scans rather than the CT scans in the evaluation of sinonasal involvement of chronic rhinosinusitis. Indeed, coronal sinus CT scan is well known to have dramatically improved the imaging of nasal cavity and paranasal sinuses¹⁴ to the point that sinus x-ray scans are no longer performed in chronic disease, mainly because they are unable to assess sinus mucosal abnormalities.^{1,6,27}

Our data allow us to observe a discrepancy between the prevalence of sinonasal disease assessed by symptom scores and the prevalence of sinus CT scan abnormalities in the overall asthmatic population. Such a situation might be explained by the presence of incidental abnormalities on CT scans of the paranasal sinuses reported in the literature regarding the asymptomatic population with rhinosinusitis.²⁸ A different pattern of paranasal sinus mucosal abnormalities was found in these asymptomatic subjects versus subjects with symptoms of sinonasal disease who showed a more frequent involvement of both the ethmoid area and the ipsilateral maxillary sinus.^{7,28} Our CT scan data confirm this pattern, which is characteristic of symptomatic patients, and furthermore show that the most significant difference evidenced by sinus CT scan in the asthmatic patients with severe versus mild-to-moderate asthma concerns the involvement of the ethmoid sinus ($P < .001$), suggesting a correlation between severity of sinonasal disease and involvement of the ethmoid area.

Finally, we found that eosinophil counts in peripheral blood show a significant direct correlation with both symptom scores and CT scan scores; this correlation is highly significant in patients with mild-to-moderate asthma and less so in patients with severe steroid-dependent asthma, possibly because of daily intake of oral corticosteroids in the latter group of patients. This result is expected because chronic rhinosinusitis is an eosinophilic syndrome,²⁹⁻³³ and peripheral eosinophilic counts are increased in this disease.¹⁴ On the other hand, association of increased peripheral blood eosinophil counts with tissue eosinophilic infiltration is well proved^{34,35}; also, recent studies, including one from our group,³⁶ describe the presence of upper airway inflammation in patients with chronic rhinosinusitis and asthma. All these data are in line with results in this article and with the leading hypothesis that rhinosinusitis and asthma are an expression of a common inflammatory process not always affected by allergy status in which eosinophils and the airway epithelium play a central role.¹²

In conclusion, this study brings further evidence that upper airway diseases is an important component of the asthma syndrome, especially of severe steroid-dependent asthma, and it shows that symptoms and image extension of sinonasal involvement are related to asthma severity. Without doubt, further investigations in this area appear to be highly desirable to achieve a better understanding and management of a condition in which quality of life is considerably impaired.³⁷

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Correction

In the article "Antigen-specific and nonspecific determinants of cytokine production during topical sensitization of mice to chemical allergens" in the August issue of the Journal (Moussavi A, Dearman RJ, Kimber I, Daniel KC, Kemeny DM. 2000;106:357-68), the incorrect version of Fig 1 was published. The correct Fig 1 with its accompanying legend appears below.

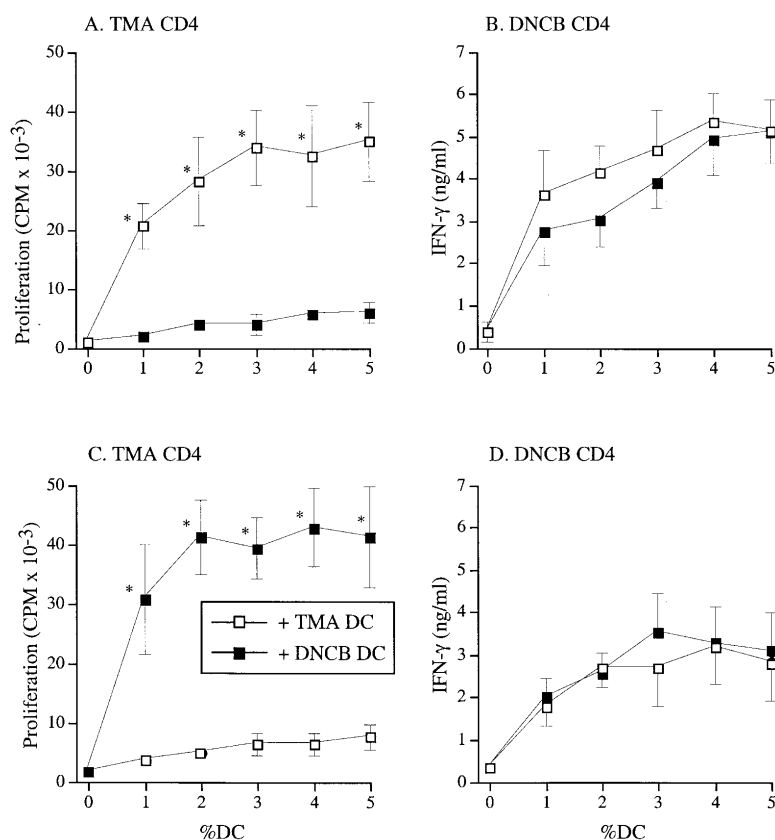


FIG 1. Proliferation and IFN- γ production by allergen-primed CD4⁺ lymphocytes cells stimulated by allergen-activated DCs. LNCs were isolated from mice 6 days after topical exposure to 10% TMA (A, B) or 1% DNCB (C, D). CD4⁺ lymphocyte populations prepared by positive selection with magnetic immunobeads were cultured with increasing numbers of either DNCB-primed DCs (solid boxes) or TMA-primed DCs (open boxes). Supernatants were harvested after 72 hours of culture and analyzed for IFN- γ content by ELISA (B, D). The remaining cells were pulsed with 1 μ Ci of tritiated thymidine for a further 18 hours (A, C). Results are expressed as the mean $\pm$ SE of 3 independent experiments. SEs are displayed only when they exceed 0.1 ng/mL or 500 counts/min. Differences versus noncognate controls were significant (asterisk, $P < .05$; two asterisks, $P < .01$, Wilcoxon single-rank test).