

SEVERE ASTHMA

The Course of Asthma in Churg–Strauss Syndrome

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Objectives. Asthma is one of the key features of Churg–Strauss syndrome (CSS); however its course in the disease is unclear. The aim of this study was to analyze the asthma course in CSS patients. **Patients and methods.** We conducted a retrospective study of 22 CSS patients. Medical documentation was studied and patients were questioned about asthma symptoms during follow-up visits, which took place at four points of the disease. These points, at which lung function tests were performed, were CSS diagnosis; introduction of treatment at hospital discharge; and assessment of the first and last clinical and laboratory CSS remissions. Asthma control and severity were assessed in compliance with current guidelines. **Results.** In the asthmatic group examined, 21 patients had an adult-onset asthma, with a mean age of onset 35.5 ± 11.8 years, preceded by sinusitis (100%) and nasal polyposis (36%). Asthma at its onset was severe in 68.5%, moderate in 27%, and very poorly controlled in 21 patients. Atopy was present in 64% of patients. Onset of vasculitic symptoms and CSS diagnosis was accompanied by high blood eosinophilia (maximal $7.2 \times 10^3/l$ [$1.2 - 32$]), asthma exacerbation with airway obstruction in 16 patients (mean values of FEV1 $68.8 \pm 17.5\%$ and FVC $84.8 \pm 19.6\%$), and lung involvement. After introducing the treatment and achieving stable remission, asthma severity/control and lung function tests (forced expiratory volume in 1 s $92.7 \pm 13.3\%$, and forced vital capacity $101 \pm 15.5\%$; $p < .001$) improved. **Conclusions.** Asthma in CSS, although severe as its onset improves after achieving CSS remission.

Keywords asthma, Churg–Strauss syndrome, lung function tests, vasculitis

INTRODUCTION

Churg–Strauss syndrome (CSS) is a rare disease with an annual prevalence of 2.7–6.8 per 1 million in the population (1). It is, however, more common in asthmatic patients, with the annual incidence of up to 64.4 per 1 million (2). The syndrome, which was first described by Churg and Strauss (3) in 1951, is characterized by a systemic, necrotizing, small- and medium-sized vessel vasculitides accompanied by blood eosinophilia, eosinophil infiltration of various tissues, and respiratory tract granuloma formation. Although the pathogenesis of CSS remains unclear, it has been hypothesized that the appearance of vasculitis is linked to asthma treatment, especially with the leukotriene receptor antagonists (LTRAs) (4), but also with inhaled corticosteroids, omalizumab, and cromolyn (5, 6). The CSS is almost always accompanied by asthma, which in most cases is severe, and precedes the vasculitis symptoms by many years (1, 7–9). Before these symptoms appear, establishing the CSS diagnosis is very difficult because both asthma and CSS share several similarities such as high blood eosinophilia, nasal polyposis, sinusitis, and allergic rhinitis. There is only one study that addresses the course of asthma in CSS patients after establishing the diagnosis, (10) and it focuses mainly on the lung function tests. This created the rationale for our study in which we retrospectively analyzed the complexity of the asthma course in CSS patients.

PATIENTS AND METHODS

Patients

We conducted a systematic retrospective study of CSS patients, who were hospitalized and diagnosed between July 1999 and March 2010 in the Department of Medicine, Jagiellonian University Medical College, Cracow, and later followed up in the outpatients clinic. The diagnosis of CSS was reassessed and confirmed according to the American College of Rheumatology (ACR) criteria (11), which distinguish six key features. The presence of four out of six criteria, namely asthma, peripheral blood eosinophilia $>10\%$, mono- or polyneuropathy, paranasal sinus abnormality, eosinophilic accumulation in tissues revealed by biopsy, and migratory infiltrates in lungs, makes the diagnosis highly probable. Our study included only those patients who fulfilled at least four of the six ACR criteria and had pulmonary function tests available for review. The medical documentation was additionally evaluated for the presence of other clinical manifestations of CSS, atopic status, history of cigarette smoking, laboratory results, and medications. The BVAS (*The Birmingham Vasculitis Activity Score* (12) range: 0–63 pts.) was used to assess the activity of CSS; results above four were assumed as active disease. All patients were asked about their asthma symptoms using a seven-item asthma control questionnaire (13), which was completed at four points in the course of the disease: at the asthma onset, at the initial diagnosis of CSS, after achieving the first clinical disease remission (which had lasted for at least 3 months), and at present—during the last CSS remission. Asthma, its severity, and level of control were classified according to the guidelines

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of National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program 2007 (14) and the current Global Initiative for Asthma guidelines (15). Besides, detailed medical data and patients' histories concerning the number of asthma exacerbations, requiring admission to hospital before CSS diagnosis, were analyzed. All patients were informed about the conducted study and signed an informed consent concerning the collection and analysis of their medical data. No approval of ethics committee was needed.

Lung Function Tests

Lung function tests were performed using standard protocols compliant with the American Thoracic Society/European Respiratory Society guidelines (16). Forced expiratory volume in 1 s (FEV1) was expressed as a percentage of predicted value, and the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio was expressed as an absolute percentage. The FEV1 <80% of predicted and FEV1/FVC ratio <70% were interpreted as airflow obstruction.

The lung function tests were performed while patients received a standard asthma treatment (with the exception of short-acting β_2 -agonists) and were evaluated at four points of the disease: at the moment of the CSS diagnosis, after introducing an intensive immunosuppressive therapy on the day of hospital discharge, after assessing the first clinical and laboratory remission of CSS, and at present (during the last remission of systemic disease).

Statistical Analysis

Statistical analysis was performed using StatSoft, Inc. (2009), STATISTICA (data analysis software system), version 9.0 www.statsoft.com. and GraphPad Prism 5.0 software (GraphPad Software, San Diego, CA, USA). Data were presented as a mean $\pm$ SD or median with interquartile range, when applicable. Comparisons of asthma severity in the course of CSS were performed by means of nonparametric Friedman test for matched quantitative values. To compare the lung function test results, Student's *t*-test for paired variables was used. P-values less than .05 were considered to be statistically significant.

RESULTS

Clinical Findings

We identified 23 patients, who were hospitalized in the years 1999–2010, fulfilling at least four ACR diagnostic criteria. One patient was excluded from this study because of severe heart failure as a main manifestation of CSS and a lack of lung function tests at the time of his diagnosis. That is why the final study group consisted of 22 patients (14 female, 8 male) aged 40.1 ± 9.5 years at the time of CSS diagnosis. Four patients fulfilled all the six criteria, 13 patients fulfilled five and five patients fulfilled four ACR criteria of CSS (Table 1). All patients had asthma, blood eosinophilia (with median maximum value of 7.2 (range 1.2 – $32 \times 10^3/\text{ml}$)), and chronic sinusitis.

TABLE 1.—Clinical characteristics of the Churg–Strauss patients

	CSS (<i>n</i> = 22)
Male : female ratio	8 (36%):14 (64%)
Age (years)	44.2 ± 9
Age at CSS diagnosis	40.1 ± 9.5
Time interval from asthma to CSS diagnosis (years)	4.9 ± 7.3
Time duration of CSS till present (years)	3.75 [0.2–10.5]
Time duration of asthma till present (years)	8.5 [1.5–34]
Atopy	14 (64%)
Chronic paranasal sinusitis	22 (100%)
Nasal polyposis	8 (36%)
Active or ex-smokers	5 (23%)
Antineutrophil cytoplasmic antibody	5 (23%)
History of LTRAs treatment	14 (64%)
Maximal blood eosinophilia, $\times 10^3/\text{l}$	7.2 [1.2–32]
Actual dose of methylprednisolone (mg)	7.3 [6–8]
Additional immunosuppressive therapy (cyclophosphamide)	15 (68%)
Biopsy proven vasculitis	5 (23%)
Peripheral neuropathy	16 (73%)
Lung infiltrates	21 (96%)

Data expressed as mean values $\pm$ standard deviation (SD) or medians [25–75 interquartile range]. CSS, Churg–Strauss syndrome; LTRAs, leukotriene receptor antagonists.

Fourteen patients (64%) were atopic, that is, had a positive allergic history accompanied by positive skin prick tests for standard inhaled allergens. Sixteen patients presented with peripheral nervous system involvement (73%), and five patients (23%) had histologically proven vasculitis. Positive perinuclear pattern of antineutrophil cytoplasmic antibodies were present in five patients (23%) (Table 1).

Following the diagnosis of their disease, all patients were treated with corticosteroids. Ten patients received an oral dose of 1–2 mg/kg/day equivalent methylprednisolone, which was gradually reduced to a minimal effective dose, or received (12 patients) intravenous pulses (500–1000 mg) on days 1–3 which was then reduced to a minimal effective dose. Fifteen patients (68%) required an additional immunosuppressive therapy (with cyclophosphamide). All patients were on inhaled corticosteroid treatment from their first asthma diagnosis and 14 patients used leukotriene receptor antagonists before CSS diagnosis.

Asthma and Pulmonary Function Tests Before and at CSS Diagnosis

All but one patient had adult onset asthma; the mean age of the onset was 35.5 ± 11.8 years. The mean duration from the onset of asthma to the moment of diagnosis of CSS was 4.9 years (range 0.1–26 years). After exclusion of four patients in whom asthma lasted for a long time (10–26 years), the mean duration in the rest was 1.8 ± 0.9 years. Based on the medical documentation and patients' answers to the questionnaires, asthma at the onset of its symptoms was classified as severe in 15 patients (68.5%), moderate in 6 (27%), and mild in 1 (4.5%) (Figure 1). Similarly, in that first period, asthma was very poorly controlled in 21 patients (95.5%). The average number of asthma exacerbations before the diagnosis of CSS was

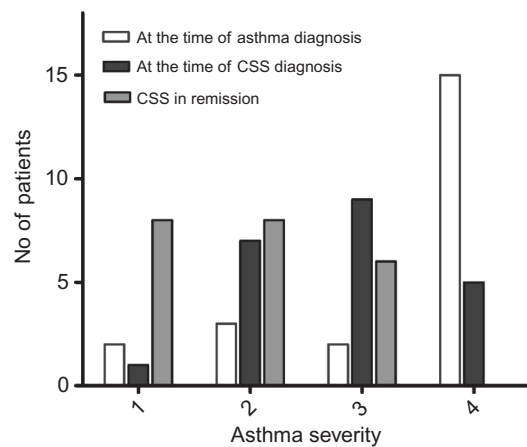


FIGURE 1.—Asthma severity in Churg–Strauss patients.

8.5 ± 7.2 and there were 3.4 ± 2.2 severe exacerbations with hospitalization. The number of exacerbations increased in consecutive years and were most frequent in the year preceding the CSS diagnosis. Despite the severity of asthma, only four patients had been treated continuously (for more than 3 months) with oral corticosteroids before CSS diagnosis, the others received them only during exacerbations. Onset of the systemic disease was accompanied by an increase in the severity of asthma in nine (41%) patients, and among these patients four had the asthmatic status. Pulmonary function tests at the time of CSS occurrence were performed in 18 patients; 4 patients due to the asthmatic status were not able to perform the tests. Airflow obstruction in available lung function tests defined as FEV1/FVC less than 70% and FEV1 less than 80% of predicted values were observed in 12 patients (mean values of FEV1 $68.8 \pm 17.5\%$ and FVC $84.8 \pm 19.6\%$). On the day of hospital discharge after introducing the immunosuppressive treatment, lung function tests were performed again and airway obstruction was still present in six patients (27.3%) with mean values of FEV1 $75.4 \pm 15\%$ and FVC $86.7 \pm 17.8\%$. The difference between the two FEV1 measurements was statistically significant ($p = .01$).

Pulmonary Function Tests at First Clinical CSS Remission

First complete and stable clinical remission of CSS (confirmed by the low BVAS and lasting for more than 3 months) was achieved in all patients after an average of 5.1 ± 1.2 months of treatment. At that moment all patients were treated with oral glucocorticosteroids with the mean daily dose of 7.2 ± 2.6 mg of methylprednisolone. In 15 patients (68%), an additional immunosuppressive therapy was continued. At this point, in none of the patients asthma was classified as severe. Twelve of them (54%) had an intermittent asthma, and in ten (46%) asthma was classified as mild (Figure 1). Lung function tests, which were performed in 22 patients, showed airflow obstruction in only two of them (9%). A significant improvement in both FEV1 (to a mean value of $89.8 \pm 17\%$) and FVC

(to a mean value of $96.4 \pm 17.1\%$) when compared with the values at the CSS diagnosis was observed ($p < .0001$ and $p < .001$, respectively).

Pulmonary Function Tests at the Last Clinical CSS Remission

After a mean duration of 8.5 years of asthma [range 1.5–34] and mean duration of diagnosed CSS of 3.75 years [0.3–10.5], in disease remission, a significant increase in both FEV1 ($92.7 \pm 13.3\%$) and FVC ($101 \pm 15.5\%$) levels was observed ($p < .001$) (Figure 2). None of the patients had airflow obstruction. Thirteen patients (59%) had an intermittent asthma, and in nine (41%) asthma was classified as mild. At that time patients were still on oral corticosteroids (the dose did not differ to the last remission), however few patients needed inhaled corticosteroids (16 patients—72%). All the patients had blood eosinophil count in normal ranges. As establishing the diagnosis and introducing the treatment only one patient had a severe exacerbation of asthma that needed hospitalization.

DISCUSSION

Our study focused on the course of asthma in CSS patients to identify possible differences from other asthmatic patients.

The natural history of CSS usually consists of three successive phases. In the first, prodromal period, allergic rhinitis appears, which is subsequently accompanied by asthma, sinusitis, and nasal polyposis; in the second stage, peripheral blood eosinophilia prevails with eosinophil tissue infiltrations, progressing into the third phase with the life-threatening vasculitis (1). Before corticosteroids were introduced for the CSS treatment, the disease was inevitably fatal. Even now, with the proper treatment at hand, the disease is characterized by serious complications (e.g., heart failure), especially when it is diagnosed late (17). Therefore, it is crucial to diagnose patients as early as possible—preferably at the first stage of the disease and to prevent complications of the vasculitic phase.

In our study, all but one patient had an adult-onset asthma before the CSS diagnosis. In almost three quarters of the patients, asthma was severe at its onset and difficult to control. These results are similar to those of Tsurikisawa et al. (9), who studied asthma before CSS development. However, in our group sinusitis (which was present in all patients) and nasal polyposis (present in one third of them) were more common than in the above-mentioned study (9). Allergy background in CSS patients remains controversial. Some studies (8, 18) are in line with our results, where allergy was common and detected in over 60% of patients, whereas in some others (9) it was less common amounting to 31.4% like in the largest and most recent one performed by Bottero's group (19). High prevalence of atopy in our group might be related to the time of testing. We performed all the tests before the vasculitic symptoms. Withdrawal of corticosteroids

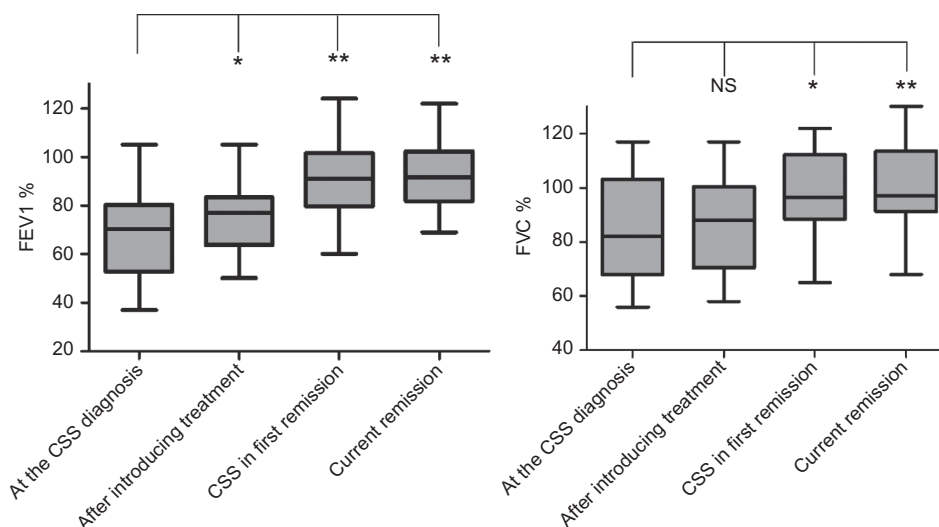


FIGURE 2.—Lung function tests in Churg–Strauss patients at the time of initial diagnosis and in remission.

In the 'at CSS diagnosis' group, four patients could not perform the lung function tests due to asthmatic status. NS, non significant. * p -values < .01, ** p -values < .001.

when CSS develops is hardly ever possible and may obscure the results of skin tests (20). Among our patients women were slightly more prevalent as observed in some prior studies (9). Features accompanying severe asthma, late onset, sinusitis, nasal polyposis, and eosinophilia, resemble a common asthmatic phenotype typical for aspirin-induced asthma (21). However, CSS patients tolerate aspirin well (22).

At the time of CSS diagnosis, an exacerbation of patient's asthma and high blood eosinophilia were seen in all patients. The exacerbation was usually severe in patients and in four of them it took a form of asthmatic status. Lung function tests revealed severe airway obstruction. These airway changes were accompanied by signs of lung involvement with parenchymal lung opacities, visualized on the chest X-ray. Lung involvement at the time of initial diagnosis is common, as previously described (23–25), and may contribute to severe abnormalities in the lung function tests and exacerbation of asthma symptoms. Following the diagnosis of CSS, all the patients received corticosteroids and, if necessary, additional cyclophosphamide (17). This treatment led to a full remission in all of the studied patients. Afterward, the course of asthma was milder with great improvement in both asthma severity/control based on the evaluation of the symptoms and lung function tests (none of the patients had FEV1/FVC below 70%). This indicates that asthma in CSS, although severe at the beginning, has a relatively favorable outcome and may not necessarily lead to irreversible airway obstruction. This finding is in contrast to the recently published study by Cottin et al. (10), who observed only a partial improvement in lung function tests, with FEV1/FVC below 70% in 50% of patients indicating an irreversible obstruction. One of the possible explanations could be that in our group, CSS followed the diagnosis of asthma by

a relatively short period of time of less than 2 years (with the exception of four patients). It is known that the prolonged asthma duration correlates with irreversible airway changes (26). In addition, corticosteroid treatment might have been introduced earlier and, by diminishing the profound eosinophilia, could limit chronic airway inflammation and remodeling (27). Both in this study and in the one performed by Cottin marked improvement in FVC parameters was recorded. This observation correlates with the previously described improvement in high resolution computed tomography in CSS patients in remission (28).

We are aware of several limitations of our study. Asthma severity and level of control that are based on symptoms may be biased by the retrospective character of this study. The assessment of asthma severity by the response to treatment is difficult to evaluate as all patients received oral corticosteroids. This study lacks lung function tests at the moment of asthma diagnosis and the studied group is relatively small.

In summary, asthma in CSS is late onset, severe from the very beginning, difficult to control, and preceded by sinusitis and nasal polyposis. Close to the time of CSS diagnosis asthma deteriorates and high blood eosinophilia is present. However, our findings suggest that after introducing treatment with systemic corticosteroid and achieving remission asthma may have an reversible character and its severity might diminish.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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