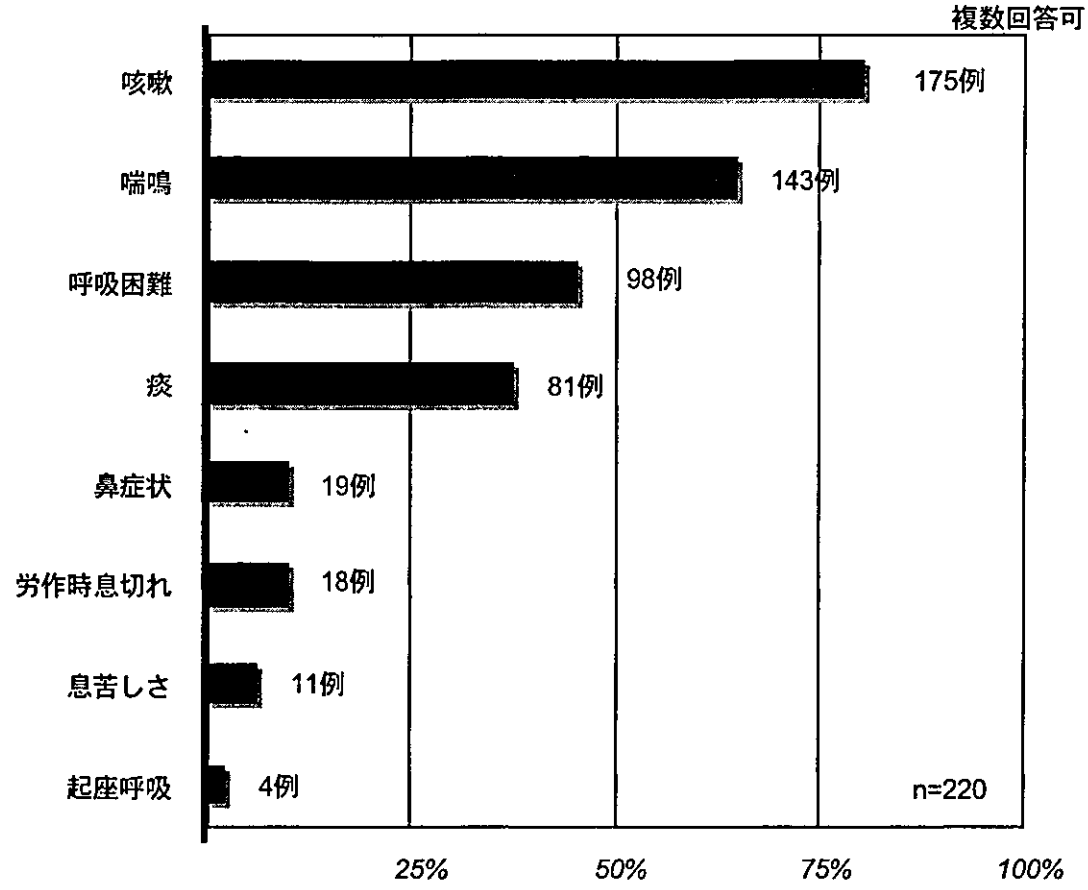
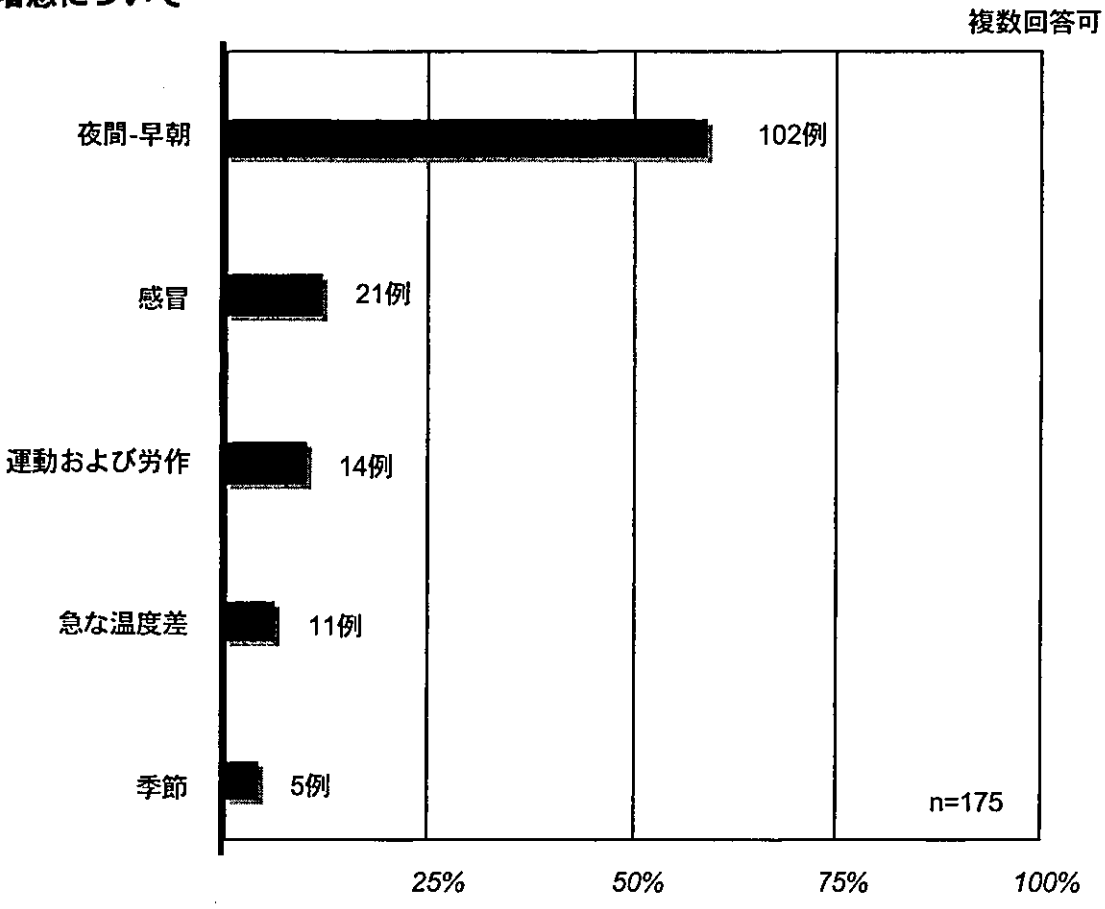
初発時の自覚症状

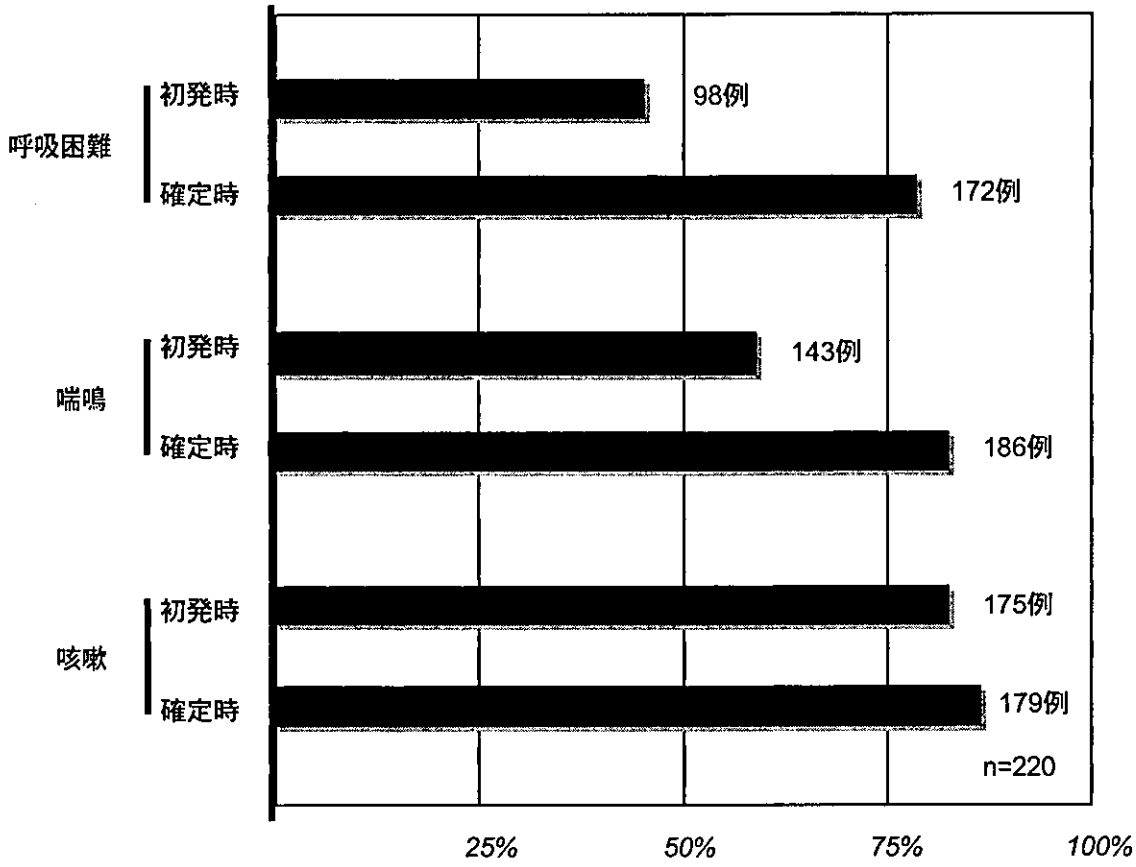


咳嗽の増悪について



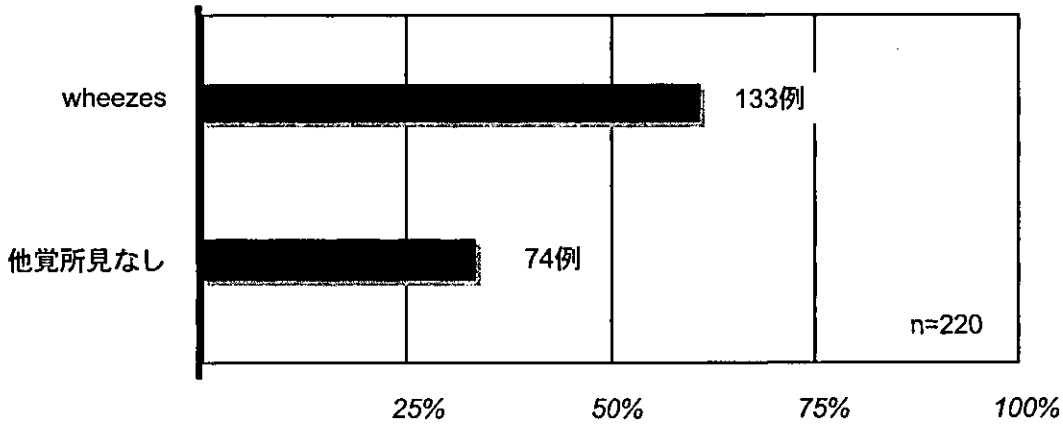
初発時と診断確定時の有症状の比較

複数回答可



診断確定時と比較し、呼吸困難、喘鳴が初発時に認めたのは、それぞれ57%、77%であった。しかし、咳嗽は初発時と確定時に差がなく、早期から出現する自覚症状と考えられる。

初診時の他覚所見



検査所見

1．末梢血好酸球

n=220

Mean ± SD : 7.0 ± 5.8%

累積(%)	%Eo
100%	40.0
75%	10.0
50%	6.0
38%	5.0
30%	3.0
0%	0.0

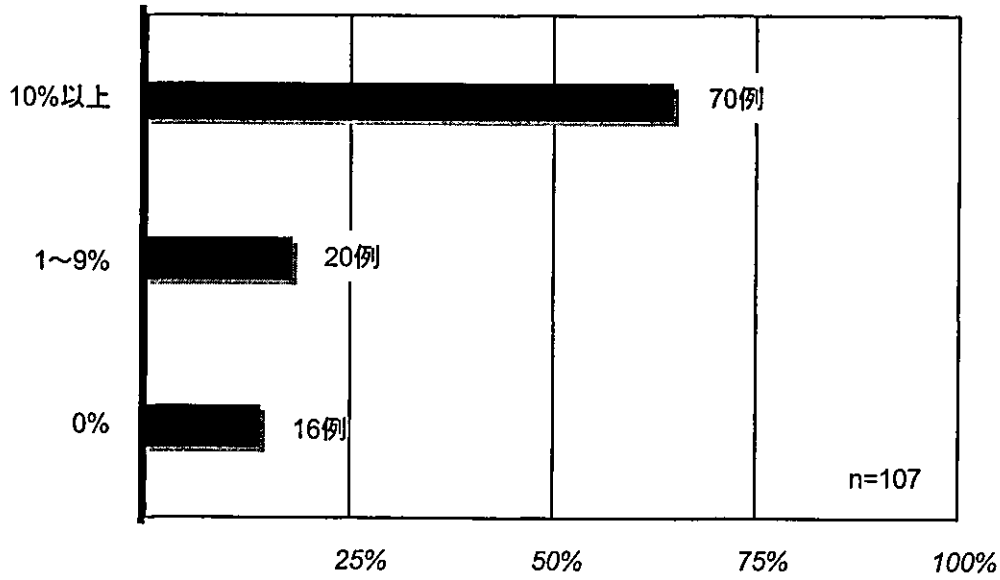
2. 血清中総IgE

n=199

Mean ± SD : 658 ± 1101 IU/ml

累積(%)	IgE
100%	8126.0
78%	1000.0
50%	249.0
15%	100.0
0%	2.0

3. 喀痰中好酸球



呼吸機能検査

1．%VC

n=148

Mean ± SD : 101.5 ± 18.0%

累積(%)	%VC
100%	178.3
50%	101.2
10%	80.3
0%	42.1

2．%FVC

n=179

Mean ± SD : 95.9 ± 20.1%

累積(%)	%FVC
100%	153.1
50%	98.1
19%	80.0
0%	32.6

3．%FEV1

n=151

Mean ± SD : 85.6 ± 20.0%

累積(%)	%FEV1
100%	130.4
75%	99.4
50%	86.5
19%	70.0
0%	30.8

4．FEV1%

n=205

Mean ± SD : 74.2 ± 13.5%

累積(%)	FEV1%
100%	100.0
62%	80.0
50%	75.6
30%	70.0
0%	28.2

5. %V50

n=156

Mean ± SD : 51.2 ± 26.2%

累積(%)	%V50
100%	135.0
98%	100.0
87%	80.0
75%	70.0
62%	60.0
0%	42.1

6. %V25

n=161

Mean ± SD : 41.4 ± 24.3%

累積(%)	%V25
100%	121.0
98%	100.0
92%	80.0
88%	70.0
78%	60.0
0%	5.2

気道反応検査

1．気道可逆性検査

FEV1% or PEFで、20%以上の改善または、FEV1で、200m l 以上の改善

n=111

気道可逆性あり＝67例（60.4%）

2. 気道過敏性検査

アストグラフまたは標準法

n=139

過敏性あり＝127例（91.4%）

まとめ

初発時に重要な症状および検査は、以下の通りであった。

1．症状

確定診断時を100％として、初発時に認められた例

98％	咳嗽
77％	喘鳴
57％	呼吸困難

2．検査

施行例を100％として、有症状例

91％	気道過敏性亢進
88％	%V25低値(70%以下)
84％	喀痰中好酸球陽性
83％	Ig-E RASTで1項目以上陽性
75％	%V50低値(70%以下)

Treatment of Churg-Strauss syndrome with high-dose intravenous immunoglobulin

Naomi Tsurikisawa, MD*†; Masami Taniguchi, MD*; Hiroshi Saito*; Hideo Himeno*; Akihiko Ishibashi*; Shunsuke Suzuki, MD†; and Kazuo Akiyama, MD*

Background: In some patients with Churg-Strauss syndrome (CSS), especially those with myocardial or neural involvement, conventional treatment with corticosteroids with or without cyclophosphamide is not effective.

Objective: To examine the effects of intravenous high-dose immunoglobulin (IVIG) in patients with CSS who showed poor responsiveness to conventional treatment.

Methods: We consecutively selected patients with CSS who showed any organ involvement despite corticosteroid treatment with or without cyclophosphamide. The diagnosis was based on the classification criteria of the American College of Rheumatology. IVIG therapy was performed with a dose of 400 mg/kg of immunoglobulin daily for 5 days. Neuropathy was evaluated with the manual muscle strength test and by the skin temperature of affected sites. Cardiac function was examined with ejection fraction by echocardiography and 2 imaging tests of myocardium (iodine 123 metaiodobenzylguanidine and thallium 201).

Results: The manual muscle strength test results were improved, and the skin temperature of both hands and legs was increased by IVIG therapy. In 5 patients with heart failure, the mean ± SD ejection fraction of the left ventricle increased from 35.2% ± 13.9% to 61.0% ± 10.1% ($P < .02$). The uptake of iodine 123 metaiodobenzylguanidine of the myocardium increased, indicating that the myocardial viability was improved. The thallium 201 images revealed the presence of perfusion defects, which were improved by IVIG therapy.

Conclusions: Patients with CSS who are resistant to corticosteroid treatment with or without cyclophosphamide may be treated effectively with IVIG therapy.

Ann Allergy Asthma Immunol. 2004;92:80–87.

INTRODUCTION

Churg-Strauss syndrome (CSS), also known as allergic granulomatosis and angiitis, is a disease involving multiple organs and characterized by bronchial asthma and peripheral blood eosinophilia. The common organ involved is the lung. Extrapulmonary lesions are seen in the cardiovascular, gastrointestinal, neurologic, skin, renal, and neurologic systems. The mainstay of treatment for CSS without organ-threatening vasculitis is systemic corticosteroid therapy.[1] Additional treatments with immunosuppressive agents, such as cyclophosphamide or azathioprine, may be used in some patients. Gayraud et al[2,3] reported that when vasculitis, such as CSS or polyarteritis, was stratified according to the Five-Factor Score (FFS), CSS patients with a FFS of 2 or higher prolonged their survival with combination therapy of corticosteroids and cyclophosphamide vs corticosteroids alone. However, some CSS patients with neuropathy and/or heart failure do not respond to combination therapy with corticosteroids and cyclophosphamide.[4–6] The mortality and prognosis of CSS are related to the disease severity, as evaluated by the FFS. In particular, the survival rate at 5 years after myocardial involvement is reported to be one third of that in cases without myocardial involvement.[7]

In 1981, Imbach et al[8] first reported on the effects of intravenous infusion of high-dose immunoglobulin (IVIG) on thrombocytopenic purpura. IVIG treatment has since been tried in a variety of autoimmune and inflammatory disorders.[9–13] To our knowledge, however, there have been only a few reports on the use of IVIG therapy for CSS. Hamilos et al[14] first reported that IVIG treatment improves eosinophilia of the peripheral blood, and other investigators[15,16] have reported that IVIG is successful in treating CSS. However, to our knowledge, there has been no study of the treatment of CSS with IVIG in more than 10 patients.

In a preliminary study, we found that when IVIG therapy was given to several patients with CSS who did not respond to combination therapy with corticosteroids and cyclophosphamide, all patients improved. In the present study, we examine the effects of IVIG treatment on CSS patients who showed poor responsiveness to treatment with corticosteroids with or without cyclophosphamide.

METHODS

Patients

From our clinic at the Clinical Research Center of Sagamihara National Hospital, Yokohama, Japan, we recruited 15 consecutive CSS patients who had responded to previous treatments with corticosteroids with or without cyclophosphamide between July 1999 and July 2001 but continued to

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Table 1. Characteristics of Patients*

Patient no./ sex/age, y	Onset of asthma, y	Onset of CSS, y	Atopy or nonatopy	Duration of CSS, mo	Prednisolone equivalent dose/cyclophosphamide, mg
1/F/56	43	54	Nonatopy	24	12.5/50
2/F/54	32	50	Nonatopy	48	40/100
3/F/70	61	66	Nonatopy	48	5/50
4/M/60	58	59	Nonatopy	3	30/50
5/F/60	57	60	Nonatopy	3	30/50
6/F/53	29	53	Atopy	3	30/50
7/F/75	59	75	Nonatopy	2	40/50
8/F/63	62	62	Nonatopy	3	40/100
9/F/75	68	69	Nonatopy	72	7.5/50
10/F/25	18	20	Nonatopy	60	15/0
11/F/58	40	58	Nonatopy	3	10/50
12/F/47	34	44	Nonatopy	32	5/50
13/M/60	57	58	Atopy	18	10/0
14/F/33†	20	21	Nonatopy	144	5/0
15/F/77	59	77	Nonatopy	2	10/0

Abbreviation: CSS, Chung-Strauss syndrome.

* Three men and 12 women participated in this study. Two were atopic and 13 were nonatopic. Mean values were as follows: age, 57.7 years; onset of asthma, 46.5 years; onset of CCS, 55.1 years; duration of CSS, 31 months; and prednisolone equivalent dose/cyclophosphamide, 19.3/13.3 mg.

† Patient 14 was initially treated with steroid pulse therapy and cardiac function was improved. After delivery, her ejection fraction gradually decreased.

have neurologic and in some cases cardiac dysfunction (Table 1). Diagnosis of CSS was made according to the classification criteria of the American College of Rheumatology[17] (Table 2). In 13 of the 15 patients, the diagnosis of CSS was histologically confirmed, and in the remaining 2 patients, the diagnosis was confirmed clinically. On entry, all patients had bronchial asthma and had been treated for a mean ± SD of 11.3 ± 7.2 years. Asthma had preceded the development of systemic vasculitis by a mean of 8.5 years (range, 1–24 years), but in 6 of the 15 patients, the onset of asthma almost coincided with the onset of systemic vasculitis. Atopic asthma (diagnosed from the positive skin test result to more than 2 allergens) was seen in only 2 of the 15 patients. Four patients (patients 4, 7, 11, and 12) had perinuclear antineutrophil cytoplasm antibody (ANCA) positivity. Before the appearance of CSS, 3 patients (patients 4, 8, and 15) had been treated with an antileukotriene antagonist (pranlukast), and 6 patients (patients 2, 3, 6, 11, 13, and 15) were in a reduction phase or had undergone withdrawal of corticosteroid therapy. The mean duration of CSS (from the start of clinical events) was 31 months (range, 2–144 months). During the CSS, all patients had neuropathy and multiple organ involvement (heart, lung, digestive organs, kidney, liver, skin, eye, sinusitis, and arthralgia). Four of the 15 patients had been treated

Table 2. Diagnosis According to the Criteria of the American College of Rheumatology*

Patient No.	Asthma	Eosinophilia	Neuropathy	Pulmonary infiltrates	Paranasal sinus abnormalities	Extravascular eosinophilia
1	O	O	O	O	O	O
2	O	O	O	O	O	O
3	O	O	O	X	X	O
4	O	O	O	O	O	O
5	O	O	O	O	O	O
6	O	O	O	X	O	O
7	O	O	O	X	O	O
8	O	O	O	X	O	O
9	O	O	O	X	X	O
10	O	O	O	O	O	X
11	O	O	O	O	X	O
12	O	O	O	O	X	X
13	O	O	O	O	O	O
14	O	O	O	O	X	O
15	O	O	O	O	O	O

* Data are from Masi et al.[17] O, present; X, absent.

with corticosteroids alone, and the remaining 11 patients had been treated with both corticosteroids and cyclophosphamide for at least 1 month before the study. In all cases, treatment with corticosteroids with or without cyclophosphamide had improved eosinophilia, eosinophilic pneumonia, skin eruption, gastric ulcer, colitis, sinusitis, arthritis, eosinophilia in urine, and/or retinal central vein occlusion. However, neuropathy and congestive heart failure due to vasculitis remained despite the resolution of other organ involvement (Table 3).

The number of involved organs in each patient varied from 2 to 7 before the therapy with corticosteroids with or without cyclophosphamide. Involvement of both the peripheral nervous system and bronchial asthma was observed in all 15 patients, and pulmonary involvement other than asthma was seen in 10 (66%) of 15 patients, digestive system involvement in 11 patients (73%), cardiovascular involvement in 5 patients (33%), sinusitis in 10 patients (67%), skin lesions in 6 patients (40%), and urinary tract involvement in 10 patients (67%). Type of neuropathy was as follows: mononeuropathy in 2 patients, polyneuropathy in 1 patient, and multiple neuropathy in 12 patients. Neuropathy of the lower extremities was observed in 15 patients and that of the upper extremities was observed in 10 patients. After the emergence of systemic vasculitis, all patients had been treated with a systemic corticosteroid (prednisolone, 0.8 mg/kg for 1 month), and cyclophosphamide was added in the case of the persistence of systemic vasculitis. The mean peripheral blood eosinophil count at the time of diagnosis was 63% and decreased to less than 5% before IVIG therapy. Before IVIG therapy, neuropathy and left ventricular failure were unchanged following treatment with corticosteroids with or without cyclophosphamide, although the involvement of other organs was much improved by treatment with corticosteroids with or without cyclophosphamide. Written informed consent was obtained from all patients.

Table 3. Organ Involvement

Patient No.	Organ involvement at onset of CSS	Organ involvement before IVIG treatment
1	N, C, L, Sk, G, Si	N, C
2	N, C, L, U, G, Si	N, C,
3	N, U, G	N
4	N, L, Sk, A, U, G, Si	N
5	N, L, U, G, Si	N
6	N, U, G, Li, Si	N
7	N, U, G, Si,	N
8	N, Sk, A, U, G, Li, Si	N
9	N, E, G	N
10	N, C, L, E, Si	N, C
11	N, L, U	N
12	N, L	N
13	N, L, Sk, Si	N
14	N, C, L, Sk, U, G	N, C
15	N, C, L, E, Sk, U, G, Si	N, C

Abbreviations: A, arthritis or arthralgia; C, cardiovascular system; E, eye; G, gastrointestinal tract; IVIG, intravenous high-dose immunoglobulin; L, lung; Li, liver; N, polyneuritis-mononeuritis multiplex; Si, sinusitis; Sk, skin; U, urinary tract.

Clinical Evaluation

We evaluated neuropathy with the manual muscle strength test using the Medical Research Council (MRC) scale (0 to 5 points). We measured the skin temperature at sites of paralysis of the hands and legs by thermography (Thermo Tracer TH1100; NEC, Tokyo, Japan) according to the method described by Coleiro et al.[18] All patients were asked to avoid alcohol for 24 hours before the study and caffeinated drinks and hot meals on the day of the test. After a baseline thermal image was obtained, both hands and legs were immersed in water at 15°C for 1 minute. Immediately after the cold challenge and 10 minutes later, thermography was performed. Rewarming was evaluated using thermograph image capture software (ThermoSoft; EIC, Jenison, MI).

Cardiac Function

In patients with heart failure only, we evaluated myocardial function. Myocardial muscle viability was examined using resting myocardial single-photon emission computed tomography (SPECT) with a 2-head camera system (Hitachi Vertex; Tokyo, Japan).[19,20] The patients underwent 2 SPECT studies using thallium 201 (^{201}Tl) and iodine 123 metaiodobenzylguanidine (^{123}I-MIBG) separately 5 to 7 days apart. The short-axis and vertical and horizontal long-axis slices were reconstructed using a Butterworth filter (cutoff, 0.56; order, 5).

The MIBG images were taken over the whole left ventricular myocardium and upper mediastinal region and used to determine the heart-to-mediastinum ratio. The washout rate of MIBG within the myocardium was measured as the percent change in left ventricular activity from early to delayed images within the left ventricular regions.

Image analysis of thallium was performed by the method of the Cedars-Sinai Medical Center.[21] Two independent observers, unaware of the clinical status of patients, evaluated cardiac thallium uptake. Semiquantitative visual interpretation was performed with short-axis and vertical long-axis myocardial tomograms divided into 20 segments for each study. The score was defined as follows: 0, normal; 1, slight reduction of uptake; 2, moderate reduction of uptake; 3, severe reduction of uptake; and 4, absence of radioactive uptake. The summed score was taken as the effect of IVIG therapy.

In echocardiography (Sonos 5500; Hewlett-Packard, Andover, MA), standard parasternal and apical views were acquired and measurements in 3 cardiac cycles were averaged by previously reported techniques.[22] The ejection fraction of the left ventricle was calculated by the multiple-disk method.[23]

Immunologic Analysis

To examine the mechanism by which IVIG treatment ameliorates CSS, we counted the number of eosinophils in the peripheral blood samples and examined the expression of CD69 molecules on the eosinophils. CD69 molecules are an activated surface marker on eosinophils and T cells and are

up-regulated earlier than the CD25 molecules.[24] Using the method of Landay and Muirhead,[25] peripheral granulocytes and mononuclear cells were incubated with fluorescein isothiocyanate–conjugated anti-human CD9 (BD PharMingen, San Diego, CA) and phico-erystine–conjugated anti-human CD69 monoclonal antibody (BD PharMingen). We analyzed the surface markers of the eosinophils by flow cytometry (FACSCalibur; Nippon Becton Dickinson, Tokyo, Japan).

IVIG Treatment

Patients were treated with IVIG (Venilon; Teijin, Tokyo, Japan) at a dosage of 400 mg/kg daily for 5 days. The use of other medications was continued without change during this study period. All patients were treated with corticosteroids with or without cyclophosphamide.

Protocol

Before the IVIG, the neuropathy of all patients was clinically evaluated by the MRC manual muscle strength test and thermography of the hands and legs, and patients with heart failure were tested with scintigraphy (^{201}Tl and ^{123}I-MIBG) and echocardiography. Blood was drawn for the immunological studies in all patients. One day after the completion of IVIG therapy, neuropathy was examined with the manual muscle strength test, and this test was repeated every week until the strength became constant. We measured the skin temperature of hands and legs at the intervals of 1 week after IVIG. In addition, we examined the effect of viability of the myocardium with SPECT myocardial scintigraphy and measured the ejection fraction with echocardiography within 2 weeks after IVIG. The patients were followed up for at least 12 months.

Statistical Analysis

All values are expressed as the mean ± SD unless otherwise specified. Statistical comparison between the groups was performed by means of a 2-way analysis of variance with repeated measures followed by a post hoc comparison using the Newman-Keuls test. Two mean values were compared using the Wilcoxon matched pairs test. $P < .05$ was considered statistically significant.

RESULTS

Treatment with IVIG improved motor neuropathy within 1 week in 13 of the 15 patients. The manual muscle strength test showed that IVIG therapy improved the muscle performance, although the conventional therapy before IVIG did not (Fig 1). In particular, 7 of the 13 patients showed an increase of 2 or more in the manual muscle strength test score. Two patients (patients 9 and 14) showed no change in motor neuropathy after IVIG. Patient 9 had severe neuropathy and significant muscle atrophy, and patient 14 continued to show slight paralysis, which had been improved by previous corticosteroid therapy. The skin temperature of the hands increased from 34.3°C ± 1.7°C to 35.7°C ± 0.5°C ($P < .01$) and that of the legs showed a similar increase from 33.1°C ± 1.2°C to 34.8°C ± 0.8°C ($P < .01$) in all 10 patients examined (Fig 2). All patients reported a sensation of warm skin after IVIG therapy.

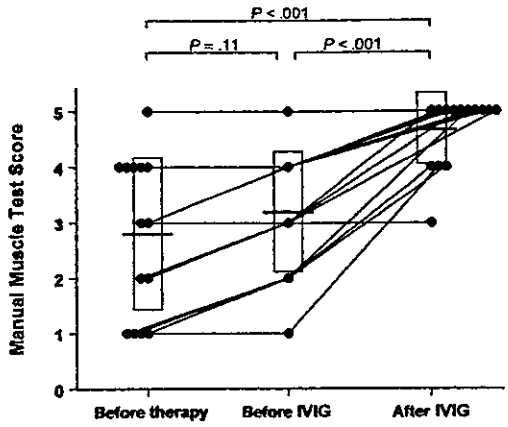

Figure 1. Manual muscle test. Before therapy indicates before treatment with corticosteroids with or without cyclophosphamide; IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD.

Cardiac function was improved by IVIG therapy in all 5 patients with heart failure. The ejection fraction of the left ventricle increased from 35.2% ± 13.9% to 61.0% ± 10.1% ($P < .02$; Fig 3). Two SPECT myocardial images of ^{123}I-MIBG and ^{201}Tl were evaluated in 5 patients before and 1 week after IVIG therapy. In all 5 patients, the myocardial uptake of MIBG was decreased before IVIG therapy. After IVIG therapy, the uptake of ^{123}I-MIBG was increased and became uniform. In quantitative analysis of ^{123}I-MIBG, the heart-to-mediastinum ratio on the delayed image increased from 1.66 ± 0.33 to 1.87 ± 0.38 by IVIG ($P < .05$), and the washout rate was also significantly improved from 51.8% ± 22.8% to 30.0% ± 16.3% by IVIG ($P < .05$; Fig 4). The ^{201}Tl images revealed the perfusion defect before IVIG therapy. In semiquantitative analysis of the ^{201}Tl image, the summed score was decreased after IVIG therapy ($P < .05$; Fig 5), indicating the improvement of blood flow perfusion. Thus,

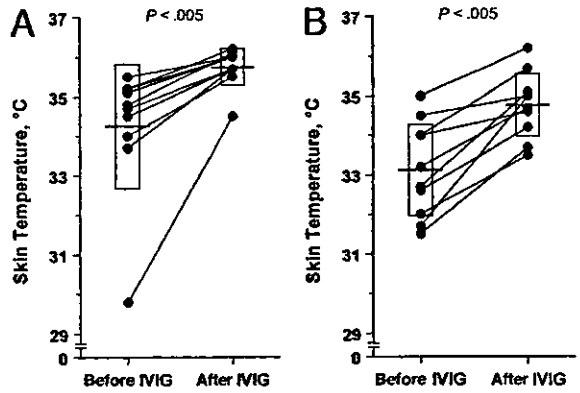

Figure 2. Skin temperature of hands (A) and legs (B). IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD.

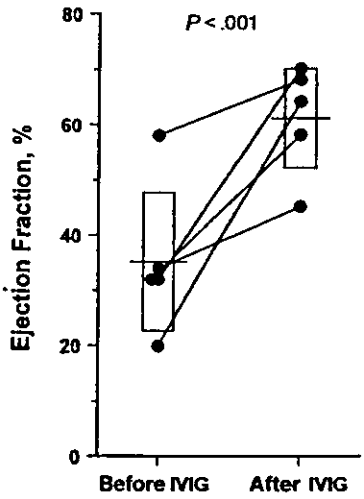

Figure 3. Ejection fraction of echocardiography. IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD.

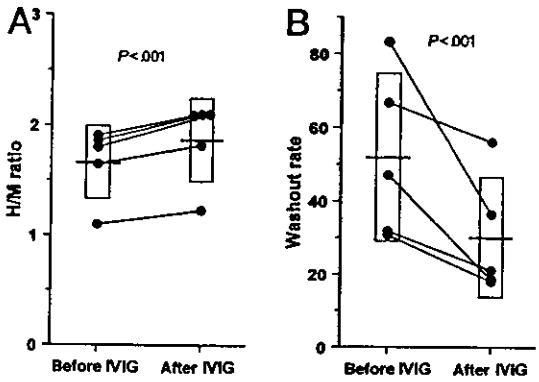

Figure 4. The heart-to-mediastinum (H/M) ratio (A) and the washout rate (B) of iodine 123 metaiodobenzylguanidine in patients with heart failure. IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD.

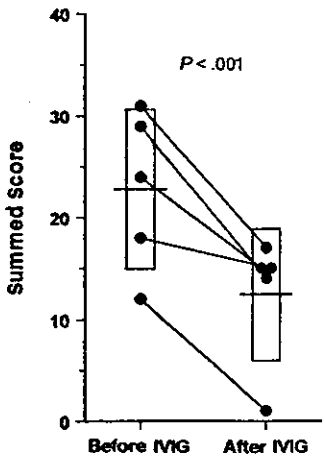

Figure 5. The summed score of thallium images. IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD.

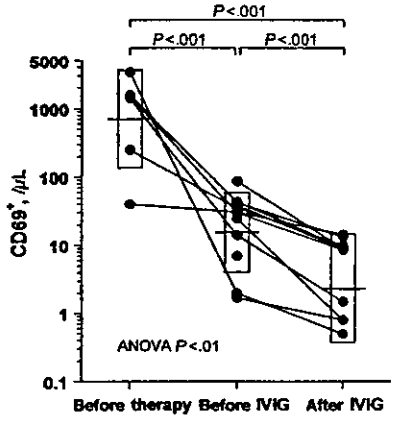

Figure 6. The effect of intravenous high-dose immunoglobulin therapy (IVIG) on CD69+ eosinophils. The CD69 cell number is expressed in a logarithmic scale. ANOVA, analysis of variance. Bars and boxes represent the mean ± SD.

IVIG treatment improved the viability of the myocardium and increased the coronary blood flow.

Eosinophils in the peripheral blood made up less than 10% of the white blood cell count after therapy with corticosteroids with or without cyclophosphamide, but the number of activated eosinophils expressing CD69 molecules was not changed by either therapy. IVIG treatment decreased the number of $CD69^+$ eosinophils from 27.5 to 5.9/μL ($P < .01$), although the number of peripheral eosinophils did not change (Fig 6).

Fortunately, none of our patients showed any significant adverse effects as a result of IVIG therapy; so we were able to continue the IVIG therapy for 5 days. Most patients were able to reduce the dose of corticosteroid to less than 12.5 mg/d (prednisolone equivalent dose) in 6 to 12 months after IVIG treatment without exacerbation of CSS.

DISCUSSION

We examined patients with CSS that was not responsive to systemic corticosteroids with or without cyclophosphamide and who had neuropathy and/or heart failure. IVIG treatment of 400 mg/kg daily for 5 days significantly improved both neuropathy and heart failure within a few weeks in these patients. We observed no significant adverse effects that required discontinuation of treatment. Neuropathy is often hard to treat with corticosteroids with or without cyclophosphamide. Heart failure is known to affect the survival rate of CSS patients.[7] Therefore, it is possible that IVIG treatment may be a second-line treatment for CSS, especially in cases of neuropathy and/or heart failure.

The disease severity of CSS, as evaluated by the FFS, is a proven predictor of disease mortality and prognosis.[2] The FFS factors consist of creatinemia, proteinuria, cardiomyopathy, gastrointestinal tract involvement, and central nervous

system involvement. An FFS of 2 or higher has been associated with a high risk of mortality.[3,7] In particular, the 5-year survival rate in patients with myocardial involvement has been reported as less than 30% for those without myocardial involvement.[7] Our patients with heart failure improved significantly. In our patients, however, the mean duration of CSS was only 13 months, and only 3 patients survived more than 5 years after treatment with corticosteroids with or without cyclophosphamide. Although the present analysis depends on the effects of neuropathy and heart failure, which were observed for 12 to 36 months, it is thus possible that IVIG may improve the survival rate via an improvement of heart failure.

Mononeuritis multiplex and sensorimotor polyneuropathy are the second most common manifestations (66%–75%).[1] Despite treatment with corticosteroids with or without cyclophosphamide, peripheral neuropathy does not often respond and is one of the major clinical problems in CSS. Richter et al[26] reported that in patients with ANCA-associated systemic vasculitis, combination therapy with corticosteroids and cyclophosphamide did not improve peripheral neuropathy. Our patients were all unresponsive to the standard therapy for CSS (ie, corticosteroids with or without cyclophosphamide), and mononeuritis multiplex and sensorimotor polyneuropathy remained. However, treatment with IVIG led to a marked improvement. After receiving IVIG, all patients but one (patient 9) showed a marked improvement of polyneuropathy. Patient 9 had neuropathy for more than 4 years; the paralysis was severe and there was significant muscle atrophy. The effect of IVIG on muscle strength appeared within several days after IVIG and persisted for 6 to 12 months. Thermography showed that all patients, including patient 9, had an increase in skin temperature. This suggests that the treatment with IVIG has a vasodilator action, resulting in an increased perfusion around neurons. In Guillain-Barré syndrome,[9] IVIG improved inflammatory polyneuropathy, although the mode of action was unclear. Therefore, it is possible that the effects of IVIG on weakened extremities might be due to similar action in neuropathy as Guillain-Barré syndrome,[9] although we have no direct evidence in the present study. Irrespective of the mechanism of IVIG, the effect of IVIG on neuropathy in CSS seems to be markedly superior to that of corticosteroids with or without cyclophosphamide.

The cardiac function of the 5 patients with heart failure remained severely damaged even after treatment with corticosteroids with or without cyclophosphamide. The echocardiographically measured ejection fraction improved markedly within 1 week by IVIG treatment. The myocardial viability also improved, as indicated by increased uptakes of both ^{201}Tl and ^{123}I-MIBG. One patient (patient 14) who had severe heart failure for at least 10 years showed a marked improvement. IVIG treatment may improve myocardial viability through an increase in vascularization and revascularization of the myocardium, as shown by the increased uptake of ^{201}Tl.[20] On the other hand, cardiac sympathetic injury was also improved, as shown by increasing postsynaptic uptake of ^{123}I-MIBG with IVIG, since the uptake of ^{123}I-MIBG shows cardiac adrenergic nerve activity as a noradrenaline analog.[27] Several reports suggest that the uptake of ^{123}I-MIBG in the lungs is a reliable marker of endothelial cell function.[28,29] It has been reported that a decrease of norepinephrine in lung extraction was related to dysfunction of pulmonary endothelial cells in humans[29] and rats.[30] Therefore, it is possible that a perfusion defect of ^{123}I-MIBG may be related to the degree of vasculitis of the heart vessels.

Imbach et al[8] first reported that high doses of immunoglobulin were effective for treatment of idiopathic thrombocytopenia. Several reports have suggested that IVIG therapy is applicable to various diseases, including multiple polyneuropathy, such as Guillain-Barré syndrome,[9] and chronic inflammatory demyelinating polyneuropathy.[10] In the early 1990s, IVIG therapy was applied to the treatment of various diseases, including microscopic polyangiitis, Wegener granulomatosis, and ANCA-associated systemic vasculitis.[12,13,16,26] There have been only a few reports, however, of the use of IVIG therapy to treat CSS. Hamilos and Christensen[14] first reported that CSS-associated peripheral eosinophilia was improved by IVIG therapy, and 2 subsequent case reports showed that IVIG therapy was effective for CSS.[15,16] Several different mechanisms have been proposed as potentially responsible for the beneficial effects of IVIG on autoimmune, inflammatory, and systemic vasculitis disorders. Fc-dependent mechanisms, such as blockade of Fcγ receptors on phagocytic cells, and inhibition of cytokines and immunoglobulin are suggested. F(ab')$_2$-dependent mechanisms may neutralize antigens, pathogens, and autoantibodies, including ANCA, and may inhibit T-cell activation.[31,32] In our CSS patients, clinical response for multiple polyneuropathy may be dependent on vasodilation and/or may be considered a direct effect by IVIG on neuron and neuromuscular junction. Basta and Dalakas[33] reported that in dermatomyositis IVIG therapy resulted in restoration of the intramuscular capillary vessels by blocking the antibody-dependent formation of C5b-9, which leads to destruction of endothelial cells. Furthermore, our patients with severe heart failure showed remarkable response in myocardial viability to the IVIG therapy. This suggests that restoration of cardiac muscle may depend on an increasing blood flow by dilation of arterioles and capillary vessels and an enhanced transmission of noradrenaline in the neuromuscular junction.

Eosinophils are the most important effector cells in CSS. It has been reported that CD69[34] and CD25[35] are surface markers of eosinophil activation expressed on eosinophils. CD69 is an acute activation marker expressed earlier than CD25, and CD69 expressed on eosinophils is activated with interleukin 3, interleukin 5, and granulocyte macrophage–colony-stimulating factor.[36,37] CD69 expression on eosinophils of the peripheral blood is observed in CSS and may be related to the eosinophil activation.[38] In all our patients, eosinophils in peripheral blood samples were decreased to less than 10% of white blood cells by treatment with corticosteroids with or without cyclophosphamide, but the expression of CD69 re-

mained unchanged. This suggests that in CSS the activated eosinophils survived even after the decrement of eosinophils by treatment with corticosteroids with or without cyclophosphamide. The IVIG therapy decreased the number of activated eosinophils, although it did not affect the cell number of eosinophils or eosinophilic cationic protein (data not shown). Therefore, the effects of IVIG therapy on CSS may occur in part through the inactivation of $CD69^+$ eosinophils.

CONCLUSION

We have demonstrated that IVIG therapy improves neuropathy and heart failure in patients with CSS. IVIG therapy may thus be useful as a second-line therapy in cases of CSS that are unresponsive to conventional therapy. The mechanisms by which IVIG therapy improves CSS may be in part the increased perfusion around neurons in neuropathy and vasodilation and enhanced neuromuscular transmission of the heart. Also, the inactivation of activated eosinophils may contribute to the improvement of CSS. In the future, double-blind randomized controlled studies will be needed, although such studies are difficult because of the limited number of CSS patients.

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Erratum

In the Table of Contents for the article "Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish school children: an international study of asthma and allergies in childhood (ISAAC) phase 2 study" (*Ann Allergy Asthma Immunol.* 2003;91:477–484) by Yıldız Saraçlar, MD, Semanur Kuyucu, MD, Ayfer Tuncer, MD, Bülent Şekerel, MD, Cansın Saçkesen, MD, and Can Kocabaş, MD, the name of author Can Kocabaş, MD, was misspelled. The printers apologize for the oversight.

Exhaled nitric oxide as a marker of airway inflammation for an epidemiologic study in schoolchildren

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Background: Exhaled nitric oxide (eNO) levels are increased in airway inflammatory disorders, such as asthma.
Objective: We sought to determine whether eNO could serve as a noninvasive marker of allergic airway inflammation for an epidemiologic study in schoolchildren.
Methods: Two hundred seventy-eight schoolchildren aged 10 to 12 years answered a modified American Thoracic Society questionnaire, and eNO levels and pulmonary function were measured. In 246 subjects serum nonspecific IgE levels and levels of IgE specific to house dust mite, cat, cedar, and mold were also measured. Correlation analysis was used to examine eNO levels, nonspecific IgE levels, antigen-specific IgE levels, and pulmonary function. In addition, we compared these variables between subjects with (recurrent wheezers) and without (nonwheezers) recurrent wheeze. Finally, multiple logistic regression analysis was used to find possible predictors for recurrent wheezers.
Results: eNO showed significant positive correlations with nonspecific IgE ($r = 0.62$, $P < .001$) and mite-specific IgE ($r = 0.74$, $P < .001$) and weak positive correlations with specific IgE to cat and cedar. Only eNO showed a weak but significant inverse correlation with pulmonary function (%FEV_1, $P = .035$; FEV_1/forced vital capacity, $P = .018$). eNO, nonspecific IgE, and mite-specific IgE levels in recurrent wheezers were greater ($P < .001$), and %FEV_1 was less ($P = .06$) when compared with values seen in nonwheezers. Finally, eNO was determined by means of multiple logistic regression analysis to be the best predictor for recurrent wheezers compared with other variables (odds ratio, 11.2; 95% CI, 1.33-94.0).
Conclusion: eNO can be used in epidemiologic studies as a noninvasive marker of allergic airway inflammation in schoolchildren. (J Allergy Clin Immunol 2004;114:512-6.)

Key words: Exhaled nitric oxide, wheeze, IgE, atopy, asthma, spirometry

In epidemiologic studies the fundamental issue of how to detect asthma and allergic airway inflammation remains unsolved. Toelle et al[1] suggested that current asthma was defined as the presence of both recent wheeze (12 months before the study) and bronchial hyperresponsiveness (BHR). However, it is unclear whether subjects with recent wheeze but no BHR have substantial airway inflammation. On the other hand, Gibson et al[2] showed that recurrent wheeze (>2 episodes per year) was a good indicator of eosinophilic bronchitis for community-based surveys because subjects with recurrent wheeze have significantly higher eosinophil counts in induced sputum. These results suggest that recurrent wheeze might be a useful predictor of allergic airway inflammation for epidemiologic studies. However, it might lack specificity because the episode of recent wheeze could occur in subjects with other disorders, such as *Mycoplasma* species, *Chlamydia* species, or respiratory syncytial virus infections.[3,4]

Abbreviations used
ATS: American Thoracic Society
BHR: Bronchial hyperresponsiveness
eNO: Exhaled nitric oxide
FVC: Forced vital capacity
NO: Nitric oxide

Exhaled nitric oxide (eNO) levels are increased in airway inflammatory disorders, such as asthma, in adults and children.[5-7] eNO in asthmatic patients is mainly produced by inducible nitric oxide synthase expressed in bronchial epithelial cells and some inflammatory cells and is reported to reflect airway inflammation.[8,9] The fact that eNO levels are increased in subjects with mild-to-moderate asthma,[5,10] increased after a late asthmatic reaction to allergens,[11] and decreased after subjects receive inhaled corticosteroids[5,12] suggests that eNO is closely associated with airway inflammation.

The aim of this study was to determine whether eNO could be used in epidemiologic studies as a noninvasive marker of allergic airway inflammation in schoolchildren.

METHODS

Study design (population and questionnaire)

Two hundred seventy-eight subjects (138 male and 140 female subjects) aged 10 to 12 years who lived in Fukushima City, Japan, were enrolled in this study. This study was completed before the start of the pollen season (February 2001) to avoid this potential confounding factor. All the subjects and their parents provided

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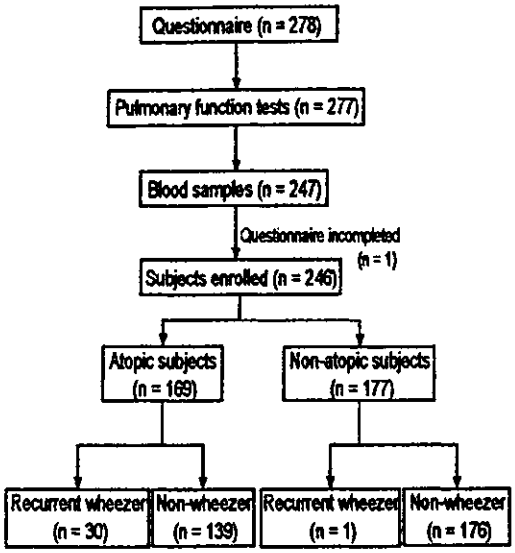

FIG 1. Number of subjects enrolled in this study.

answers to a modified American Thoracic Society (ATS) questionnaire, as published in 1978.[13] According to this questionnaire, subjects who reported wheeze more than 2 times in the previous 24 months were defined as *recurrent wheezers*, and subjects who had never wheezed were classified as *nonwheezers*. Children with recurrent wheeze were considered to have probable asthma. All subjects provided written informed consent, and the local ethics committee approved this study.

Nitric oxide measurement

eNO was measured according to the ATS recommendations[14] with a chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, Colo) and defined in parts per billion. The analyzer provides online continuous measurement of nitric oxide (NO) in a single exhalation with a detection range of 0.1 to 500 ppb. Environmental NO was measured before and after each study and never exceeded 5 ppb. All subjects were studied in the sitting position without wearing a nose clip. Subjects exhaled at a constant flow rate (50 mL/s) from total lung capacity to residual volume without breath holding. Subjects maintained a constant mouth pressure (17 cm H_2O) by monitoring a visual display[14] to eliminate contamination from nasal NO. Dead space and nasal NO (which are reflected by the NO concentration peak during exhalation) and NO from the lower respiratory tract (determined by the plateau value after the peak) were recorded automatically by using the manufacturer's software. Three eNO measurements of the plateau phase were obtained, with less than 10% variation. The mean value of 3 successive reproducible recordings was retained for statistical analysis. The eNO measurement was taken before pulmonary function testing.

Pulmonary function tests

Pulmonary function tests were performed with rolling seal spirometers (CHESTAC-11 CYBER S-type; Chest M.I., Inc, Tokyo, Japan). FEV_1 and forced vital capacity (FVC) were measured according to the ATS guideline[13] by well-trained pulmonary technicians; and the best of 2 or 3 technically acceptable maneuvers reproducible to within 100 mL was retained. Values for FEV_1 and FVC were expressed as percentages of the predicted value for statistical analysis.[15]

Allergy screening

Specific IgE to house dust mite, cat, cedar, and mixed molds (*Penicillium*, *Aspergillus*, *Cladosporium*, *Alternaria*, *Candida*, and *Helminthosporium* species) were assessed by using a RAST, and nonspecific IgE levels were determined by means of fluorescence enzyme immunoassay (UniCAP; Pharmacia & Upjhon, Uppsala, Sweden). Antigen-specific IgE concentrations of more than 0.69 UA/mL were regarded as positive RAST results. Subjects were characterized as atopic if they had at least one positive RAST result or a nonspecific IgE level of 250 IU/mL or greater.

Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 8.0; SPSS, Chicago, Ill). eNO, nonspecific IgE, and specific IgE were log normally distributed in the population, and therefore these data were log transformed for statistical analysis. Mean data were expressed as geometric means and 95% CIs. Correlations among eNO, nonspecific IgE, specific IgE, and pulmonary function (%FEV1, %FVC, and FEV_1/FVC) were made by using Spearman rank analysis. The comparison of each parameter between recurrent wheezers and nonwheezers was made with the Student *t* test. Finally, multiple logistic regression analysis was performed to assess the most useful parameters for differentiating recurrent wheezers and nonwheezers. The odds ratio was used to measure the relative risk for recurrent wheezers, and a 2-tailed *P* value of less than .05 was considered significant.

RESULTS

Characteristics of the subjects

Fig 1 shows the number of subjects enrolled in this study. All the subjects answered the modified ATS questionnaire. Of these, 277 subjects underwent eNO measurement and pulmonary function tests. Furthermore, 247 of 277 subjects provided blood for analysis. Finally, the data from 246 subjects were analyzed for this study because one subject failed to answer the questionnaire completely. Of these 246 subjects, 31 (12.6%) had recurrent wheeze. Moreover, 23 (74.2%) of these 31 subjects were previously given diagnoses of asthma. There were 6 subjects who were treated with a short-acting β_2-agonist, xanthine, or an antiallergic drug, but they did not use them within 18 hours before the measurements. In addition, none of the subjects had ever received inhaled or oral corticosteroids. On the other hand, 169 (68.7%) subjects had atopy; 30 of them were recurrent wheezers, and 139 of them fell into the nonwheezer group.

Relationship among eNO, serum IgE, and pulmonary function

Fig 2 shows the relationships between eNO and IgE. eNO showed strong positive correlations with nonspecific IgE ($r = 0.623$, $P < .001$) and specific IgE to house dust mite ($r = 0.774$, $P < .001$). In addition, it also showed weak positive correlations to cedar-specific IgE and cat-specific IgE ($r = 0.169$, $P = .008$; $r = 0.297$, $P < .001$, respectively). The average level of eNO was 37.2 ppb (95% CI, 33.1-41.9) in atopic subjects and 15.3 ppb (95% CI, 13.6-17.1) in nonatopic subjects. eNO levels of atopic subjects were significantly higher than those of nonatopic subjects ($P < .001$).

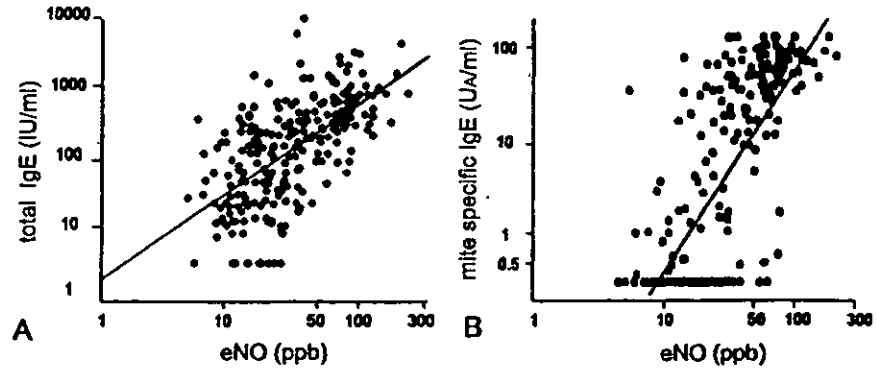

FIG 2. A, Relationships between eNO and total IgE levels (A) and eNO and mite-specific IgE levels (B).

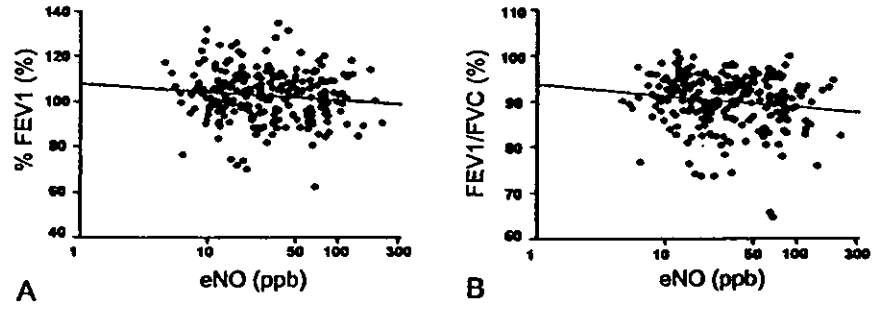

FIG 3. A, Relationships between eNO and %FEV_1 (A) and eNO and FEV_1/FVC (B).

Fig 3 shows the relationships between eNO and pulmonary function. eNO showed weak but significant negative correlations with %FEV_1 ($r = -0.127, P = .035$) and FEV_1/FVC ($r = -0.150$, $P = .018$). However, there was no significant correlation between eNO and %FVC ($r = -0.055$, $P = .361$). We could not detect any significant correlation between IgE and pulmonary function (data not shown).

Comparison between recurrent wheezers and nonwheezers

eNO levels, nonspecific IgE levels, and levels of IgE specific to house dust mite were significantly greater in recurrent wheezers ($P < .001$). In addition, %FEV_1 tended to be less in recurrent wheezers ($P = .06$, Table I). However, specific IgE to cedar and cat, which showed significant correlations with eNO, showed no significant difference between recurrent wheezers and nonwheezers.

The average level of eNO was 60.3 ppb (95% CI, 46.8-79.4) in recurrent wheezers, 33.3 ppb (95% CI, 29.4-37.8) in atopic nonwheezers, and 15.1 ppb (95% CI, 13.5-17.0) in nonatopic nonwheezers. All recurrent wheezers except for one subject had atopy, and the eNO level of the subject without atopy in this group was 31.4 ppb. eNO levels of recurrent wheezers were significantly higher, regardless of atopy, than those of nonwheezers ($P < .001$, Fig 4).

Results of multiple logistic regression analysis

Table II shows the final results of multiple logistic regression analysis and the best indicator for differentiating between recurrent wheezers and nonwheezers. Eleven parameters shown in Table II were included in this analysis. Results of the analysis indicated that eNO was the most useful parameter to differentiate recurrent wheezers and nonwheezers (odds ratio, 11.2; 95% CI, 1.33-94.0; $P = .03$).

DISCUSSION

Study of a large sample of schoolchildren shows that a standard method for eNO measurement[14,16] can be performed easily and properly and used as a noninvasive marker of allergic airway inflammation. The average eNO level was 28.2 ppb (95% CI, 25.4-31.2) in all subjects, 60.3 ppb (95% CI, 46.8-79.4) in recurrent wheezers, and 15.1 ppb (95% CI, 13.5-17.0) in nonatopic nonwheezers. Previously reported eNO levels were highly variable and probably caused by differences in the method used to measure eNO.[17] In this study we measured eNO at a constant flow rate of 50 mL/s, maintaining a constant mouth pressure of 17 cm H_2O according to ATS and ERS recommendations.[14,16] With this standardized method, we

TABLE I. Comparison of individual parameters

	Recurrent wheezer (n = 31)	Nonwheezer (n = 215)	*P* value
Age (y)	11.4	11.4	.56
Sex (male/female)	15/16	109/106	.81
Height (cm)	149.1 (146.6-151.6)	149.1 (148.1-150.1)	.98
Weight (kg)	40.9 (38.3-43.5)	42.3 (40.8-43.7)	.34
eNO (ppb)	60.3 (46.8-79.4)	25.2 (22.7-27.9)	<.001
Total IgE (IU/mL)	459 (292-721)	106 (85.1-133)	<.001
Mite-specific IgE (UA/mL)	32.5 (18.6-56.8)	2.39 (1.75-3.26)	<.001
Cat-specific IgE (UA/mL)	0.54 (0.39-0.74)	0.42 (0.37-0.46)	.11
Cedar-specific IgE (UA/mL)	1.54 (0.92-2.57)	0.94 (0.76-1.16)	.10
Mold-specific IgE (UA/mL)	0.36 (0.29-0.45)	0.34 (0.32-0.36)	.50
FVC (% predicted)	99.1 (95.3-103)	98.1 (96.8-99.5)	.60
FEV_1 (% predicted)	97.2 (93.6-101)	101 (99.7-103)	.06

Data are expressed as geometric means and 95% CIs.

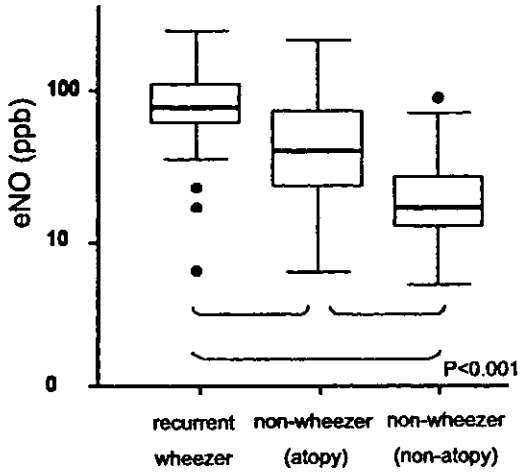

FIG 4. Comparison of eNO levels from recurrent wheezers and nonwheezers with or without atopy. Box plots for eNO levels by subject group are shown. The *thick bar* is the median value, and the *shaded box* represents the interquartile range. Outlying points beyond the inner fences are shown individually.

TABLE II. Multiple logistic regression analysis (association with recurrent wheeze)

	Adjusted OR	95% CI	*P* value
Log (eNO)	11.2	1.33-94.0	.03
Log (mite-specific IgE)	2.28	0.90-5.78	.08
Sex	1.83	0.75-4.45	.19
Log (mold-specific IgE)	1.21	0.16-9.33	.86
Log (cedar-specific IgE)	1.10	0.54-2.24	.79
Height	1.01	0.93-1.10	.82
Weight	0.99	0.94-1.05	.80
FEV_1 (% predicted)	0.97	0.93-1.01	.12
Log (total IgE)	0.96	0.26-3.53	.95
Log (cat-specific IgE)	0.92	0.29-2.93	.89
Age	0.56	0.26-1.22	.14

Data are expressed as adjusted odds ratios and 95% CIs.
OR, Odds ratio.

measured eNO levels similar to those seen in previous reports.[18,19] These results suggest the importance of standardization of the measurement method when eNO is applied to an epidemiologic study.

eNO is strongly correlated with nonspecific IgE and specific IgE to house dust mite. Our results are similar to those of Moody et al,[20] who found that increased eNO levels were associated with house dust mite sensitivity in asymptomatic Pacific Islanders. In addition, Henriksen et al[21] found that there were some correlations between eNO and IgE RAST scores for indoor allergens in subjects who do not have symptoms such as wheeze and BHR, suggesting that atopy itself might increase eNO levels. However, in this study we also observed a weak but significant negative correlation between eNO versus %FEV_1 and FEV_1/FVC and found no correlation between pulmonary function versus total IgE and mite-specific IgE levels. Previous studies revealed some controversy in the relationship between eNO and pulmonary function. Some authors failed to find a relationship between eNO and pulmonary function.[22,23] However, the sample size was relatively small in these studies, and the standardized method was not applied. On the other hand, a recent study by Strunk et al[10] revealed a relationship between eNO, measured by means of standardized methods, and FEV_1/FVC in subjects with mild and moderate asthma. Furthermore, Djukanovic et al[24] reported that some atopic subjects without symptoms and BHR had airway eosinophilic infiltration, degranulation of eosinophils, and subepithelial collagen deposition. From these considerations, it seems reasonable to assume that eNO is linked to atopy and its associated airway pathology, such as allergic airway inflammation.

Recurrent wheeze and BHR have been used frequently to detect asthma and airway inflammation for epidemiologic screening. However, the relationship between eNO and BHR is not understood well. In population studies by Salome et al[25] and Henriksen et al,[26] levels of eNO were higher in subjects with recent wheeze and BHR. However, once asthma becomes symptomatic, BHR persists in most asthmatic subjects treated with high-dose corticosteroids, even when the degree of airway inflammation improves.[27] These facts indicate that although BHR is a good marker of asthma, it might not be a direct marker of airway inflammation.[28-30] On the other hand, it is unclear whether any significant airway abnormality exists in the subjects with recurrent wheeze. Gibson et al[2] showed that subjects

with recurrent wheeze have significantly higher eosinophil counts in induced sputum, and Stevenson et al[31] also demonstrated that atopic children with recurrent wheeze present ongoing airway inflammation represented by eosinophil and mast cell recruitment in bronchial lavage fluid studies. These studies indicate that recurrent wheeze might be a good marker of airway inflammation. In this study we found that eNO levels, nonspecific IgE levels, and levels of specific IgE to house dust mite were greater and $\%FEV_1$ was less in recurrent wheezers. Furthermore, we found that eNO was the most useful marker to detect recurrent wheezers. These results, together with the results of studies mentioned above, suggest that eNO can be used as a sensitive marker reflecting allergic airway inflammation.

Other markers to detect airway inflammation are the number of eosinophilis in induced sputum or bronchoalveolar lavage fluid and mucosal eosinophilic infiltration by fiberoptic bronchial biopsies.[32,33] However, these methods are too invasive and laborious for use in epidemiologic studies and unsuitable for use, especially in children.

In conclusion, the results of this study suggest that eNO can be measured easily and properly in schoolchildren, can be used in epidemiologic studies, and represents a useful noninvasive marker of allergic airway inflammation.

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FcεRI-mediated amphiregulin production by human mast cells increases mucin gene expression in epithelial cells

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Background: Topical application of a glucocorticoid is now widely recognized as the first-line therapy for bronchial asthma. However, glucocorticoid treatment is largely ineffective in relation to overproduction of sputum and lung tissue remodeling.

Objective: The purpose of the current study was to identify human mast cell (MC) products that are related to goblet cell hyperplasia.

Methods: The FcεRI-mediated gene expression profile of MCs was examined by using high-density oligonucleotide probe arrays and RT-PCR. Secretion of a protein, amphiregulin, by the MCs was measured by ELISA. Upregulation of mucin genes in NCI-H292 cells by amphiregulin was evaluated by real-time RT-PCR. The expression levels of amphiregulin on histological sections obtained from 40 subjects with asthma and 6 healthy control subjects were estimated by immunohistochemical staining, and the correlation with the number of goblet cells was studied.

Results: Amphiregulin was secreted by human MCs after aggregation of FcεRI, and its expression was not inhibited by a glucocorticoid (dexamethasone). Amphiregulin upregulated mucin gene expression in airway epithelial cells. Upregulation of amphiregulin expression was observed in MCs of patients with asthma, but not normal control subjects. Furthermore, upregulation of amphiregulin in MCs significantly correlated with the extent of goblet cell hyperplasia in the mucosa of patients with bronchial asthma.

Conclusion: These results suggest that after exposure to antigens, human MCs may induce sputum production via release of amphiregulin. Therefore, amphiregulin may be a new target molecule for treatment of overproduction of sputum in bronchial asthma. (J Allergy Clin Immunol 2005;115: 272-9.)

Key words: Mast cells, amphiregulin, bronchial asthma, goblet cell hyperplasia, dexamethasone

Bronchial asthma is characterized physiologically by variable airflow obstruction and airway hyperresponsiveness. Goblet cell hyperplasia has been established as a pathologic characteristic of mild, moderate, and severe asthma.[1] Abnormalities in goblet cell numbers are accompanied by changes in stored and secreted mucin.[1] Mucus hypersecretion is often a marked feature, particularly in status asthmaticus. The presence of mucus hypersecretion was associated with a significantly greater decline in FEV_1.[2] Topical application of a glucocorticoid is now widely recognized as the first-line therapy for bronchial asthma. Although treatment with steroids has been reported to prevent the development of allergen-induced goblet cell hyperplasia in animal models,[3] it has less effect once goblet cell hyperplasia has been established.[4] Furthermore, in human beings, treatment with a corticosteroid is largely ineffective in relation to tissue remodeling and mucus production, both pathologically[5] and clinically. Currently, there are no drugs that exert a specific action on mucus production.

Sensitized and allergen-exposed animals develop marked goblet cell hyperplasia.[4,6] The pathogenesis underlying allergen-induced goblet cell hyperplasia in mice is thought to involve a variety of mediators, including IL-4,[7] IL-13,[8,9] IL-9,[10] the epidermal growth factor (EGF) system,[11] a disintegrin and metalloprotease family,[12] and ion channels such as gob-5[13] (hCLCA1 in human beings[14]), probably by upregulating the expression of mucin genes. The major effector cell is thought to be the T_H2 subtype of $CD4^+$ lymphocytes. However, allergen-challenge high-affinity receptors for IgE (FcεRI)–knockout mice showed less airway inflammation, less goblet cell hyperplasia, and lower levels of IL-13 in lung homogenates compared with the controls.[15] Furthermore, IL-9 but not IL-4 or IL-13 increased mucin gene expression in a human airway epithelial cell culture system.[16] We

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