A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan

Ken-Ei Sada1, Koichi Amano2, Ritei Uehara3, Masahiro Yamamura4, Yoshihiro Arimura5, Yoshikazu Nakamura3, and Hirofumi Makino1; for the Research Committee on Intractable Vasculitides, the Ministry of Health, Labour, and Welfare of Japan

1Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, 2Division of Rheumatology/Clinical Immunology, Department of Medicine, Saitama Medical Center, Saitama Medical University, Saitama, Japan, 3Department of Public Health, Jichi Medical University, Tochigi, Japan, 4Center for Rheumatology, Okayama Saiseikai Hospital, Okayama, Japan, and 5First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Abstract
Objective. We conducted a cross-sectional nationwide survey to determine eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) prevalence and clinical features in Japan.

Methods. Data for EGPA patients were collected from 1,564 hospitals. In total, 965 patients were reported from 365 departments. In a second survey, clinical data for 473 patients were obtained. We estimated that 1,866 (95% CI: 1,640–2,092) patients have EGPA in Japan (prevalence, 17.8/1,000,000). Of the 473 patients in the second survey, 315 fulfilled American College of Rheumatology (ACR) criteria or Lanham’s criteria for EGPA. The mean age (±SD) of the 315 at onset was 55 ± 14 years, male to female ratio 1:2. 93% of patients had neurological manifestations, which were the organ system most frequently involved. Among 277 patients tested for myeloperoxidase (MPO)/p anti-neutrophil cytoplasmic antibody (ANCA), 139 (50%) were positive, while only 6 of 238 were positive for proteinase3 (PR3)-/cANCA. MPO-ANCA-positive patients had renal involvement, mucous membrane or ophthalmological symptoms, and ENT symptoms more frequently, whereas cutaneous lesions and cardiovascular involvement were less common.

Conclusion. The prevalence of EGPA and the frequency of MPO-/p-ANCA-positivity in Japanese EGPA patients were mostly similar to those of Western countries. However, female predominance and a high frequency of neurological manifestations characterized Japanese patients.

Introduction
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), originally described as allergic granulomatosis and angiitis, is characterized by pulmonary and systemic small-vessel vasculitis, extravascular granulomatous, and hypereosinophilia, and occurs in individuals with asthma and allergic rhinitis [1]. EGPA is a rare vasculitis, and its prevalence in the USA and Europe ranges from 10.7 to 13 per 1,000,000 adults, depending on the classification criteria used [2–4]. In most epidemiological studies, ACR criteria [5] and Lanham’s clinical criteria [6] have been used for classification of EGPA. The epidemiology and clinical features of EGPA in Japan have been reported by limited institutions; however, no nationwide studies based on these classification criteria have been performed at present.

EGPA is often associated with the presence of ANCA that are mostly targeting MPO, whereas other pathogenic mechanisms are also involved in the pathogenesis of EGPA [7]. In the USA and Europe, less than 50% of patients have circulating MPO-ANCA [8]. Recent studies have suggested the existence of different disease subsets in EGPA; for example, ANCA-positive patients have more clinical and histopathological features of small-vessel vasculitis, whereas ANCA-negative patients show tissue infiltration of eosinophils [8]. Previous reports showed that microscopic polyangiitis (MPA) with positive MPO-ANCA was more common in Japan, while granulomatosis with polyangiitis (Wegener’s) (GPA) with positive PR3-ANCA was more common in the UK [9]. Although the predominance of ANCA-positivity in Asian patients with EGPA remains to be determined, this could have an effect on the clinical features of their disease progression.

Here, we report the results of a cross-sectional nationwide survey, conducted in 2009, describing the prevalence and clinical features of Japanese patients with EGPA.

Materials and methods
This survey was designed in the form of two sequential investigations. The first survey was for the epidemiological study, which investigated only the number of patients with EGPA who were treated at hospitals in Japan during 2008, and the second survey was for the clinical study in which a questionnaire was sent to only the departments that had treated EGPA patients during 2008.

The list of all hospitals in Japan was obtained from the Ministry of Health and Welfare. The hospitals were categorized according...
to the institution type and the number of hospital beds. Hospitals were randomly selected from these categories; sampling rates were determined as approximately 5%, 10%, 20%, 40%, 80%, and 100% for the stratum of general hospitals with 20–99 beds, 100–199 beds, 200–299 beds, 300–399 beds, 400–499 beds, and 500 or more beds, respectively [10]. From this selection, 2,599 hospitals were selected. Then, in January 2009, the first questionnaire was sent mainly to the department of internal medicine, rheumatology, and neurology at the 2,599 hospitals asking only the number of patients with EGPA treated during 2008. A total of 1,564 hospitals responded to the questionnaire, reporting having treated 965 patients with EGPA in 365 medical departments.

Next, the second survey questionnaire asking for detailed clinical features of each patient was sent only to the departments that reported treating patients with EGPA in 2008. In this study, EGPA was classified by ACR and Lanham’s criteria, based on the European Medicines Agency algorithm for the classification of ANCA-associated vasculitis and polyarteritis nodosa [11], and these criteria were used to evaluate the clinical manifestation of EGPA. The following information was examined in the questionnaire: age, sex, history of allergic diseases, previous treatment for allergic diseases, existence of typical clinical course (manifestations of small-vessel vasculitis developed within several years after the onset of allergic diseases), histological information, Birmingham Vasculitis Activity Score (BVAS) [12] at the onset of the disease and the last visit, eosinophil number, ANCA positivity, and treatment information. Details of clinical manifestations and organ involvement were recorded with a corresponding date using the nine items listed on the BVAS form [12] (Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.857582). From the initial 965 patients, clinical data on 475 patients from the second questionnaire were returned. However, two patients were excluded due to insufficient data, leaving a total of 473 patients who were enrolled in this study. The Ethical Board of Jichi Medical University approved this survey (October 2008, No. 08-35).

All statistical analyses were performed using the JMP Statistical Package for Windows software, version 8.0 (SAS Institute Inc., Cary, NC, USA). All results were expressed as means ± SD.

We estimated the prevalence of EGPA from results of the first survey. The estimation was based on the assumption that the responses of the departments were independent of the frequency of patients [13]. The estimation of prevalence of EGPA was computed as

$$\hat{a}_k = \frac{1}{SRT_k \cdot RRT_k} \sum_i n_i N_e \cdot \frac{1}{n_k} \sum_i n_i N_k, \quad \hat{a}_k = \frac{n_k}{N_k} \sum_i n_i N_k$$

where $SRT_k$, $RRT_k$, $N_k$, $n_k$, $N_e$ and $N_{ed}$ denote the sampling rate, response rate, the number of sampling departments, the total number of departments, the number of responding departments, and the number of departments with $i$ patients in stratum $k$, respectively [14].

Differences in clinical features between MPO-/p-ANCA-positive and -negative patients in categorical variables were determined by Fisher’s exact test. The prevalence ratios (PRs) of organ involvement and the associated 95% CIs were also determined. $P$-values of less than 0.05 were considered significant for all statistical analyses.

**Results**

**Prevalence of EGPA in Japan**

Of the 2,599 hospitals selected from all over Japan, 1,564 responded to the first questionnaire concerning the number of EGPA patients treated during 2008. A total of 965 patients from 365 medical departments were reported to have been treated for EGPA. Therefore, the annual number of patients treated for EGPA was 1,866 (95% CI: 1,640–2,092). From these results, we calculated the prevalence to be 17.8 per 1,000,000.

**Patients’ characteristics**

Of the 473 patients whose clinical data was made available from the second survey, 315 (67%) patients fulfilled the ACR criteria or Lanham’s clinical criteria for EGPA. The clinical characteristics of 315 patients fulfilled the ACR criteria or Lanham’s clinical criteria for EGPA are shown in Table 1. The mean age (± SD) was 55 ± 14 years, and the male to female ratio was 1:2. Among the 277 patients tested for MPO-/p-ANCA, 139 (50%) patients were positive for MPO-/p-ANCA at diagnosis, while 138 patients were negative. On the other hand, PR3-/c-ANCA tests were positive in only 6 (3%) of the 238 patients who were tested for PR3-/c-ANCA.

The biopsy of 206 of 315 EGPA patients showed eosinophil infiltration in 139 patients (67%), necrotizing vasculitis in 58 patients (28%), and extravascular granulomas in 17 patients (8%).

The clinical manifestations of EGPA in 315 patients are shown in Table 2. Overall, 93% of patients had neurological manifestations, which was the most common system involved. In addition, systemic, skin, respiratory system, and renal involvements were found in 76%, 51%, 60%, and 39% of patients, respectively. In contrast, ENT symptoms and cardiovascular involvement were reported in only 23% and 16% of patients, respectively.

A total of 303 (96%) patients were treated with glucocorticoids (mean dosage of prednisolone: 46 ± 13 mg/day), and 94 (30%) of these patients were treated with a combination of glucocorticoids and immunsuppressive agents. Patients responded well to these treatments, and organ manifestations had mostly improved by the final visit. However, neurological manifestations, defined by the persistence of BVAS, still remained in 42% of patients. Cardiovascular and renal manifestations were 15% and 12%, respectively.

**Table 1. Demographic data and clinical characteristics of 315 patients with eosinophilic granulomatosis with polyangiitis.**

| N     | 315 |
|-------|-----|
| Age at onset (years) | 55 ± 14 |
| Male/Female | 103/209 |
| Asthma, N (%) | 308 (98) |
| Allergic rhinitis, N (%) | 41 (13) |
| Treatment employed before the presentation of vasculitic manifestations |
| Glucocorticoid therapy, N (%) | 215 (68) |
| Oral corticosteroids, N | 82 |
| Inhaled corticosteroids, N | 183 |
| Leukotriene receptor antagonists, N (%) | 132 (48) |
| Typical clinical course before onset*, N (%) | 207 (66) |
| Eosinophil number (μL) | 11494 ± 9172 |
| MPO-/p-ANCA positive, N (%) | 139/277 (50) |
| PR3-/c-ANCA positive, N (%) | 6/238 (3) |
| Tissue biopsy performed, N (%) | 206 (65) |
| Skin, N | 120 |
| Peripheral nerve, N | 60 |
| Kidney, N | 19 |
| Gastrointestinal tract, N | 14 |
| Muscle, N | 13 |
| Lung, N | 11 |
| Paranasal sinus, N | 4 |
| Others, N | 6 |

ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, peroxidas-3.

Eosinophilic granulomatosis with polyangiitis was defined by ACR and Lanham’s criteria for all 315 patients.

*Typical clinical course means symptoms due to vasculitis follow allergic disease and eosinophilia.
Table 2. Clinical features of 315 patients with eosinophilic granulomatosis with polyangiitis.

| N | %  |
|---|----|
| **Systemic** | 238 | 76 |
| **Skin** | 162 | 51 |
| **Mucous membranes/Eyes** | 31 | 10 |
| **ENT** | 72 | 23 |
| **Chest** | 190 | 60 |
| **Cardiovascular** | 50 | 16 |
| **Abdominal** | 50 | 16 |
| **Renal** | 122 | 39 |
| **Nervous system** | 293 | 93 |

ENT, ear, nose, and throat. Eosinophilic granulomatosis with polyangiitis was defined by ACR and Lanham’s criteria for all 315 patients.

Differences in clinical features between ANCA-positive and -negative patients

We analyzed the data of the clinical findings that had been collected from EGPA patients through the 2nd survey questionnaire, which applied the nine items subcategories on BVAS for determining the clinical findings. The clinical features of 139 MPO-/p-ANCA-positive EGPA patients were compared with those of 138 MPO-/p-ANCA-negative patients. In MPO-/p-ANCA-positive patients, renal involvement, mucous membranes or ophthalmological symptoms, and ENT symptoms were more frequent at diagnosis than in ANCA-negative patients (PR, 95% CI: renal 1.8, 1.3–2.5; mucous membranous or eye 2.5, 1.1–5.4; and ENT 1.7, 1.1–2.7; Table 3 and Figure 1). On the other hand, ANCA-positive patients had fewer skin lesions and cardiovascular involvement than ANCA-positive patients (PR, 95% CI: skin 0.8, 0.6–1.0; and cardiovascular 0.6, 0.3–1.0).

Discussion

Here, we report the results of a cross-sectional nationwide survey on EGPA in Japan. To our knowledge, this study was one of the largest epidemiological studies of EGPA that has been published worldwide, and the results demonstrated that the estimated prevalence of EGPA in Japan was 17.8 per 1,000,000 adults, which was similar to the prevalence reported for the USA and other countries in Europe (10.7–13 per 1,000,000 individuals) [3,4]. In this study, twice as many women had EGPA as men, with a male to female ratio of 1:2. In contrast, previous studies in the USA and Europe have reported a male to female ratio of around 1:2. Since the female predominance was also seen in several clinical studies for MPA in Japan [18–20], this difference in sex distribution may indicate potential environmental and/or genetic influences on the pathogenesis of ANCA-associated vasculitis.

The clinical features frequently found in Japanese EGPA patients included neurological (93%), skin (51%), and respiratory system (58%) involvement. Consistent with this finding, previous reports have indicated that the frequencies of peripheral and central nervous system involvement, pulmonary abnormalities, and cutaneous lesions ranged from 65% to 76%, 51% to 96%, and 40% to 57%, respectively [8,15–17,21]. However, the greater prevalence of neurological manifestations in our study may suggest that mononeuritis multiplex is the most characteristic clinical feature of Japanese EGPA. On the other hand, ENT symptoms were less common than in previous studies, which ranged from 48% to 77% [8,15–17,21]. In the present study, we determined the presence or absence of ENT symptoms judged from the results of BVAS item lists. Therefore, asymptomatic or mild nasal and paranasal sinus diseases may be overlooked, and, furthermore, no surveys from the departments of otorhinolaryngology in our study may eventually resulted in the low frequency of ENT symptoms.

Several reports from Asian countries have shown MPO-/p-ANCA and MPA predominance in patients with ANCA-associated vasculitis, in contrast to the predominance of PR3-/c-ANCA and GPA in Europe and the USA [9,22]. Our study showed that the proportion of EGPA patients who had MPO-/p-ANCA at the onset of EGPA was almost 50%, and this frequency was some higher as compared with the previous reports, in which MPO-/p-ANCA had been detectable in less than 40% [8,16]. In present study, 277 of the 315 patients were tested for MPO-/p-ANCA. Since patients with vasculitic symptoms were highly more detectable for MPO-/p-ANCA than patients without such symptoms, the higher frequency of ANCA positivity may be simply due to more patients with vasculitic EGPA that had been preferentially recruited in our study than in previous reports. MPO-/p-ANCA-positive patients exhibited renal involvement, mucous membrane or eye involvement, and ENT symptoms more frequently than ANCA-negative patients. Furthermore, recent clinical studies have shown that ANCA-positive EGPA patients probably have organ manifestations associated with small-vessel vasculitis, such as focal segmental glomerulonephritis, peripheral neuropathy, purpura, and subcutaneous nodules [16]. Since involvement of the kidneys and mucous membranes or eyes is often seen in MPA and GPA, these results are consistent with those of previous studies. However, the higher prevalence of ENT symptoms in MPO-/p-ANCA-positive patients has not been found in previous studies. Chen et al. showed that MPO-ANCA-positive patients with GPA are common in Chinese populations [23], while PR3-ANCA-positive patients with GPA are common in European populations [24]. Bottero et al. suggested that both rhinitis and asthma in EGPA patients sometimes lack the allergic feature that is usually found in non-EGPA asthmatic patients [25]. Combined with the fact that a history of allergic ENT symptoms in Japanese EGPA patients was less common, this may indicate that ENT symptoms in Asian patients are caused by vasculitis rather than allergies.

In contrast, ANCA-negative EGPA patients exhibited more cardiovascular involvement than ANCA-positive patients. Cardiac involvement is one of the most important predictors of adverse outcomes in EGPA and has been reported to be the primary cause of death in earlier studies, with frequencies up to 50% [6,26]. Of the patients with myocardial manifestations, 39% died during the early stages of the disease [26]. Moreover, although 49% of EGPA patients had cardiovascular involvement as defined by BVAS in a previous report [8], only 16% of EGPA patients...
patients had cardiac involvement in our study. In addition, chronic cardiac disorders, as defined by persistent BVAS at the final visit, were rarely found. It was recently reported that 62% of EGPA patients showed cardiac abnormalities during remission using a combination of clinical evaluations, ECG, echocardiograms, and cardiac MRI [27]. However, the findings of another study support our results, reporting a similar prevalence of cardiac disorders as defined by BVAS [16]. Therefore, asymptomatic cardiac involvement may have been detected more frequently during careful examinations in our patients. In addition, it is possible that a subset of EGPA patients with poor prognostic factors was excluded from our study because this survey was cross-sectional and required an observation period of 1 year.

A limitation of this study was that the prevalence of EGPA, as determined by the first survey, was measured based on the diagnosis of the physician involved, rather than a standard classification (e.g., ACR criteria or Lanham’s criteria). Since only 67% of patients fulfilled the standard classifications, we may overestimate the prevalence of patients with EGPA. On the other hand, we may underestimate the EGPA prevalence, because failed to collect the patient data from the department of pulmonology and otorhinolaryngology in the selected hospitals, where a significant part of Japanese patients with EGPA had to be treated.

In conclusion, the prevalence of EGPA and ANCA in Japan were similar to those previously reported for the USA and Europe. However, recent studies showed MPO-/p-ANCA predominance and a high MPA to GPA incidence ratio in Japanese patients with ANCA-associated vasculitis. The female predominance and increased occurrence of neurological manifestations may be significant features unique to Japanese EGPA patients.

Acknowledgements

The authors would like to thank all the participants and physicians who supported this nationwide survey of EGPA in Japan.

Funding

This work was supported in part by grants from the Ministry of Health, Labour and Welfare of Japan (nannti-ippan-004).

Conflict of interest

None.

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Supplementary material available online

Supplementary Appendix.