Concise report

Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK

Shouichi Fujimoto¹, Richard A. Watts², Shigeto Kobayashi³, Kazuo Suzuki⁴, David R. W. Jayne⁵, David G. I. Scott⁶, Hiroshi Hashimoto⁷ and Hiroyuki Nunoi⁸

Abstract

Objectives. The epidemiological manifestations of ANCA-associated vasculitis (AAV) differ geographically. However, there have been no prospective studies comparing the incidence of AAV between Japan and Europe over the same time period using the same case definitions.

Methods. The incidence of AAV was determined by a population-based method in Miyazaki prefecture, Japan, and Norfolk, UK, between 2005 and 2009. Patients with AAV were defined and classified according to the European Medicines Agency (EMEA) algorithm.

Results. The number of incident cases of AAV in Japan and the UK were 86 and 50, respectively, and the average annual incidence over the 5-year period was 22.6/million (95% CI 19.1, 26.2) and 21.8/million (95% CI 12.6, 30.9) in Japan and the UK, respectively. The average age was higher in patients in Japan than in patients in the UK [mean (median), 69.7 (72) vs 60.5 (61) years]. Microscopic polyangiitis (MPA) was the predominant subtype in Japan (83%), while granulomatosis with polyangiitis (Wegener’s) was more frequent in the UK (66%). As for the pattern of ANCA positivity, >80% of Japanese patients were pANCA/MPO positive, whereas two-thirds of UK patients were cANCA/PR3 positive. Renal involvement in MPA was very common in both countries, but was much less common in granulomatosis with polyangiitis in Japan compared with the UK.

Conclusion. There was no major difference in AAV incidence between Japan and the UK, but this prospective study found MPA and MPO-ANCA to be more common in Japan and granulomatosis with polyangiitis and PR3-ANCA to be more common in the UK, in line with earlier reports.

Key words: Microscopic polyangiitis, Granulomatosis with polyangiitis (Wegener’s), Churg-Strauss syndrome, Myeloperoxidase anti-neutrophil cytoplasmic antibody, Proteinase 3 anti-neutrophil cytoplasmic antibody, Incidence, Epidemiological study.

Introduction

Geographical differences in the epidemiology of the vasculitides have been observed. Takayasu arteritis and Kawasaki arteritis are more common, but GCA is less common in Japan compared with European and/or North American countries. As for ANCA-associated vasculitis (AAV), the incidence of granulomatosis with polyangiitis (Wegener’s) is higher than that of microscopic polyangiitis (MPA) in northern Europe [1–3]. On the other hand, MPA is predominant among cases of AAV in southern Europe [4]. However, some recent papers have indicated that the incidence of MPA cannot be correlated with latitude [5, 6]. In Japan, the prevalence of MPA and/or renal limited...
vasculitis (RLV) has been reported to be much higher than granulomatosis with polyangiitis by a hospital-based nationwide survey [7]. However, there have been no studies investigating the incidence, rather than the prevalence, of AAV in Japan and comparing the clinical features of AAV between Japan and Europe or the USA up to the year 2005.

To elucidate the potential differences in the incidence and clinical phenotype of new-onset AAV, an international collaboration study was started in 2004. In 2005, before the epidemiology study in Japan, UK members visited Miyazaki prefecture to inspect the medical facilities and survey the population and advised Japanese members to conduct a population-based survey of AAV. The first study was performed as a retrospective study in renal units in Miyazaki prefecture from 2000 to 2004 and revealed that the estimated annual incidence of primary renal vasculitis was 14.8/million [8]. Watts et al. [9] compared the incidence of renal vasculitis prospectively determined in Norfolk, UK, with Miyazaki, Japan, and reported that the overall occurrence of renal vasculitis was similar between the two countries, but the clinical phenotypes were very different, with MPA predominating in Japan and granulomatosis with polyangiitis predominating in the UK.

Epidemiological studies on potential differences of AAV in the world are useful to investigate the aetiology and pathogenesis as well as to inform genetic and therapeutic studies of AAV. This study was planned to clarify the epidemiological differences between Japanese and European patients with AAV.

**Subjects and methods**

**Japanese population**

This study was done between 1 January 2005 and 31 December 2009 in five renal, three rheumatology and two otolaryngology units, which are the only referral centres for new-onset cases of AAV [MPA, granulomatosis with polyangiitis and Churg–Strauss syndrome (CSS)] in the western, southern and central area of Miyazaki prefecture. Each unit prospectively registered new-onset cases of AAV, and one investigator (S.F.) collected and reviewed the data from all centres each year. The population in these areas seldom undergoes medical examinations in the other prefectures. The populations of adults (aged >15 years) and seniors (>65 years old) in these areas comprised 759,000 (male, 47.5%) and 220,000 persons, respectively, in 2009. The study population was relatively static and we estimated the total immigration rate out of the study area during 2005–2009 to be <2%. The study obtained ethical approval in each country (Ethical committees of the University of Miyazaki Hospital, Miyazaki, Japan, and University of East Anglia, Norwich, UK).

**UK population**

Since 1988 the Norfolk and Norwich University Hospital (NNUH) has maintained a prospective register of its patients with AAV, as previously reported [10]. This institution is the single, central referral centre for a stable and ethnically homogeneous population of ~500,000. The study area covers a geographically isolated coastal region in eastern England, allowing the population to be well defined and therefore suitable for epidemiological studies over a prolonged period of time. The estimated 2009 population was 459,000 (males 48.1%). Around 20.9% of the population is aged >65 years, which is higher than the average for England generally (15.9%) (Office for National Statistics, www.statistics.gov/).

**Classification of vasculitis**

Patients with AAV were defined and classified according to the European Medicines Agency (EMEA) algorithm [10]. This uses an algorithm to classify vasculitis and utilizes the American College of Rheumatology (ACR) criteria (1990) and the Chapel Hill Consensus Conference definitions. Using this approach, RLV is placed within MPA.

**Determination of ANCA specificities**

ANCA was determined by IIF and by ELISA for PR3/MPO specificity using commercially available kits. A comparative study of the ELISA kits used in Europe and Japan demonstrated close correlations in specificity and sensitivity [11].

**Statistical analysis**

Continuous data were presented as the means (s.d.). Annual incidences were presented as simple proportions with 95% CIs, and calculated using the Poisson distribution. Comparisons between the Japan and UK studies were made using the chi-square test for dichotomized variables and unpaired t-test for continuous variables. Values of $P < 0.05$ were considered statistically significant.

**Results**

Table 1 shows the incidence, clinical phenotype and ANCA subtypes of AAV in Japan and the UK. In Japan, the numbers of incident AAV were 14, 21, 18, 19 and 14 in the years 2005, 2006, 2007, 2008 and 2009, respectively. The average annual incidence of AAV over the 5-year period was 22.6/million adults (95% CI 19.1, 26.2). On the other hand, in the UK, the numbers were 14, 5, 11, 15 and 5 in each year, and the annual incidence per million adults was 21.8 (95% CI 12.6, 30.9). The male-to-female ratios were identical in Japan and the UK, but the average age was significantly higher in Japan compared with the UK [69.7 (11.0) vs 60.5 (14.8) years, $P < 0.001$], and the difference in the median age was ~10 years. However, the mean ages in the patients with MPA or granulomatosis with polyangiitis were not different between the two countries [MPA, Japan ($n = 69$) vs UK ($n = 15$), 71.6 (10.0) vs 68.7 (13.3) years, $P = 0.333$; granulomatosis with polyangiitis, Japan ($n = 8$) vs UK ($n = 33$), 61.4 (9.9) vs 56.9 (15.2) years, $P = 0.440$]. As for seniors, the annual incidence was 57.0/million and 47.9/million in Japan and the UK, respectively. In both areas, the annual incidence of MPA was about 10 times higher in seniors compared with younger adults (from 15 to 64 years old). Among patients with AAV, MPA was the predominant type in Japan [annual incidence 18.2 (95% CI
granulomatosis with polyangiitis was predominant in the UK [annual incidence 14.3 (95% CI 5.8, 23.0)]. There were also significant differences in the pattern of ANCA positivity. More than 80% of Japanese patients were pANCA/MPO positive, whereas two-thirds of UK patients were cANCA/PR3 positive.

Table 2 shows the comparison of clinical features between the two countries. ENT and respiratory involvements were more common in the UK compared with Japan. Renal involvement in MPA was very common in both countries, but was much less common in granulomatosis with polyangiitis in Japan compared with the UK. Respiratory involvement in granulomatosis with polyangiitis was also less common in Japan than the UK.

### Discussion

A geographical difference in the incidence of AAV has been suggested [1–4]. We previously reported that the clinical phenotype and ANCA specificities of primary renal vasculitis were quite different between Japan and the UK [8, 9]. Previously there were no cases of granulomatosis with polyangiitis/PR3-ANCA detected in Miyazaki, now there have been six cases of granulomatosis with polyangiitis and eight cases of PR3-ANCA diagnosed in Japan. The previous retrospective survey was conducted only in the renal units, whereas the present prospective study was performed in rheumatology and otolaryngology units that are the referral centres for the cases of AAV (with or without renal involvement) in addition to renal units. This may be the reason behind the discrepancy between the two studies. The present prospective study revealed for the first time that the incidence of AAV was similar between Japan and the UK, but MPA was predominant in Japan, whereas granulomatosis with polyangiitis was more common in the UK among patients with AAV. The characteristics of the profiles of patients with AAV in Miyazaki, Japan, were as follows: (i) 80% had MPA, (ii) 84% were pANCA/MPO positive, (iii) the mean and median ages (70 and 72 years) were high and (iv) renal and respiratory involvements in granulomatosis with polyangiitis were less common.

Latitude may affect geographical differences in the incidence of AAV. European studies have shown that granulomatosis with polyangiitis is more common in high-latitude areas than low-latitude areas. For example,
the incidences of granulomatosis with polyangiitis and MPA are 10.5 and 2.7/million, respectively, in Tromsø, Norway (latitude 70° north) [12], 7.9 and 2.7/million, respectively, in Schleswig-Holstein, Germany (latitude 51° north) [3] and 3.0 and 7.9/million, respectively, in Lugo, Spain (latitude 43° north) [4]. There have been no reports regarding the incidence of granulomatosis with polyangiitis in areas more southern than latitude 40° north, but the latitude of Miyazaki prefecture, which is on Kyushu, the southernmost of the four major islands of Japan, is almost 30° north. The incidence of granulomatosis with polyangiitis has not yet been clarified in other areas in Japan, but data from our 1998 nationwide survey showed that the annual prevalence of patients with granulomatosis with polyangiitis was very low compared with that of MPA (granulomatosis with polyangiitis 2.3/million and MPA 13.8/million) [7]. Environmental factors and very different triggers at different latitudes may affect the occurrence of different clinical phenotypes. On the other hand, Gatenby et al. [5] recently described an inverse association between latitude [low regional ambient ultraviolet (UV) radiation] and the incidence of granulomatosis with polyangiitis, but not MPA. Vitamin D levels are low at high latitudes; polymorphisms in vitamin D receptor-binding genes are common in individuals of European and Asian descent, and this may explain the distribution of multiple sclerosis and other autoimmune diseases, which tend to occur with increased frequency at higher latitudes [13].

Race differences and/or genetic backgrounds might also contribute to the proportions of the AAV and/or ANCA subtypes. In a US cohort study, Caucasians comprised >90% of all granulomatosis with polyangiitis patients, whereas African Americans, Hispanics and Asians together represented only 1–4% of patients [14]. The population in the European studies consisted exclusively of Caucasians [1–3, 12]. On the other hand, in a study of 426 patients from China, 20% were classified as having granulomatosis with polyangiitis and 80% as having MPA, and only 16% were cANCA/PR3 positive [15]. Among Japanese patients with MPA and/or RLV, 79–93% are positive for MPO-ANCA [7], compared with 44–69% of European patients [4, 16]. Genetic differences between the two populations may explain the observed differences. For example, European population substructure studies have shown that people from northern and southern Europe have different genetic backgrounds [17]. Our previous multicentre collaborative study demonstrated that HLA-DR0901 is much more prevalent among MPA/MPO-ANCA-positive patients than in healthy controls [18]. Another example is RA, which occurs in both Europe and Japan, but with a different genetic background: PTNP22 polymorphism is strongly associated with RA in Europe, but the PTNP22 polymorphism does not occur in the Japanese population [19]. However, appropriate international studies using standardized methods of classification and genetic profiling have not been performed. For this reason, the results of recent joint studies undertaken by the European Vasculitis Study Group (EUVAS), the ACR and the Japanese government in order to define new classifications and diagnosis criteria are greatly anticipated [20].

The average age of patients with AAV was significantly higher in Japan compared with the UK, whereas the average age of patients with MPA or granulomatosis with polyangiitis was not different. The annual incidence of MPA was about 10 times higher in seniors compared with young adults in both countries. Considering these findings, we think that the reason for a substantial difference in the mean age between the two countries is due to the large number of patients with MPA in Japan.

MPA patients without renal involvement were much less common in both countries. On the other hand, in the UK, granulomatosis with polyangiitis was more common, and the majority of these patients had ENT, respiratory and renal involvement. In the previous retrospective epidemiological study of primary renal vasculitis performed in Miyazaki prefecture in 2000–2004, no renal vasculitis patients with granulomatosis with polyangiitis were seen [8]. Only three granulomatosis with polyangiitis patients with renal involvement were found in the present study from 2005 to 2009. Taken together, the results from the 10-year span of these studies suggest that renal involvement in granulomatosis with polyangiitis may be much less common in Japan than in the UK.

The incidence of CSS has fallen dramatically in the UK compared with earlier reports from the Norfolk area [2]. We do not think it is due to a change in classification, as we have carefully reclassified all our patients according to the EMEA algorithm [10]. It could be due to a change in environmental factors, but we do not know which ones, or due to the treatment of asthma with newer drugs, making it less likely that the patient will develop CSS. In conclusion, the clinical features and ANCA specificities of AAV were quite different between Japan and the UK. To clarify whether the different aetiologies and genetic backgrounds may affect the occurrence of different clinical phenotypes in various populations, international collaboration studies using the same methodology will be needed.

**Rheumatology key messages**

- The incidence of AAV did not differ between Japan and the UK.
- MPA was the predominant subtype in Japan, while granulomatosis with polyangiitis was predominant in the UK.
- The serum MPO/PR3-ANCA ratio in AAV patients was much higher in Japan than the UK.

**Acknowledgements**

We would like to thank Dr S. Uezono of Miyazaki Prefectural Hospital; Dr S. Hisanaga of Koga General Hospital in Miyazaki; Dr T. Tokura of Miyazaki Konan Hospital; Dr K. Umekita, Dr A. Okayama, Dr S. Hirahara and Dr T. Tono of the University of Miyazaki; and
Dr T. Hidaka of Shiminomori Hospital in Miyazaki for their kind collaboration in this study.

Funding: This work was supported in part by grants from the Ministry of Health, Labor and Welfare, Japan (H21-General-004 and 20260401).

Disclosure statement: The authors have declared no conflicts of interest.

References


