Original article

The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis

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Abstract

Objectives. Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are uncommon and have unknown aetiology. The aim of the study was to investigate the epidemiology of GPA and MPA in a stable, well-defined population looking for differences in the pattern of occurrence, which might suggest a different aetiology.

Methods. Since 1988, we have maintained a prospective register of all patients with systemic vasculitis attending the Norfolk and Norwich University Hospital. Patients presenting with new-onset GPA and MPA as defined by the European Medicines Agency algorithm and registered with general practitioners in the former Norwich Health Authority area between 1988 and 2010 were identified. The population in 2008 was estimated to be 459 000 (221 000 males).

Results. One hundred and eleven GPA and 58 MPA incident cases were identified during 1988–2010. The overall annual incidence of GPA and MPA was 11.3/million and 5.9/million, respectively. There was evidence of a cyclical pattern of occurrence with a periodicity of 7.6 years for GPA with a peak incidence of 28.3/million in 2005 and the lowest in 2002 (2.2/million). Other lesser peaks occurred in 1990 and 1996. While the peak incidence of MPA was in 2008 (15.2/million), there was no convincing evidence of periodicity. The incidence of cANCA/PR3- or pANCA/MPO-positive vasculitis showed a similar pattern to GPA and MPA, respectively.

Conclusion. This study lends support to the notion that the aetiology of GPA and MPA may be distinct conditions with different aetiologies. The cyclical incidence of GPA is possibly an indication for the influence of infection.

Key words: granulomatosis with polyangiitis (Wegener's), Wegener's granulomatosis, microscopic polyangiitis, epidemiology, vasculitis.

Introduction

The ANCA-associated vasculitides (AAVs) granulomatosis with polyangiitis (Wegener's) (GPA) [1] and microscopic polyangiitis (MPA) are relatively uncommon conditions

characterized by the development of necrotizing vasculitis (in particular, affecting the kidney) and the presence of ANCAs in serum. Despite this similarity, there are differences between GPA and MPA. GPA is characterized by necrotizing vasculitis, granulomata formation, upper respiratory tract involvement and the presence of ANCA targeted against the PR3 antigen. MPA more characteristically involves the lower respiratory tract and is associated with ANCA directed against MPO. The aetiopathogenesis of GPA and MPA is unknown, but is widely thought to involve the interaction of environmental factors with a genetically predisposed host.

Environmental factors such as infection and drug exposure have been investigated as potential risk factors

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for both GPA and MPA [2]. Infections have not been shown to be associated with the onset of either disease. Nasal carriage of *Staphylococcus aureus* has been associated with the relapse of GPA but not MPA [3]. Infection with fimbriated bacteria has been associated in a small study with the occurrence of renal vasculitis [4]. Drug exposure, for example with hydralazine or propylthiouracil, typically induces vasculitis associated with anti-MPO antibodies rather than anti-PR3 antibodies [5]. Thus there are suggestions that environmental factors may be different for the two conditions.

Epidemiological studies also provide an opportunity to investigate the action of genetic and environmental factors in determining the occurrence of these two conditions. We have shown differences in the occurrence of GPA and MPA between the UK and Japanese populations [6]. The possibility of an infectious aetiology can also be addressed by examining for the evidence of periodicity; however, to date, few studies have accrued enough data to permit this type of analysis.

The Norfolk Vasculitis Register (NORVASC) was established in 1988 and has since then prospectively identified all patients with AAV who attend the Norfolk and Norwich University Hospital (NNUH). This is the central referral hospital for a stable ethnically homogenous population of ~500 000. The NORVASC register thus provides the opportunity to study long-term changes in incidence and prevalence of GPA and MPA from a geographically well-defined population. We now present data from the longest prospective epidemiological study of GPA and MPA, looking for the evidence of periodicity in their occurrence.

Methods

All patients attending the NNUH as outpatients, day admissions and hospitalized with a new clinical diagnosis of GPA and MPA between 1 January 1988 and 31 December 2010 were identified prospectively using methods described previously [7]. Patients from the denominator population (defined below) were identified. A retrospective review of the complete case notes was performed to confirm the diagnosis of GPA and MPA.

Patients with a documented onset of GPA and MPA prior to 1988 were excluded, as were patients living outside the denominator population and those with other types of systemic vasculitis: Churg–Strauss syndrome, PAN, HScP, HV and vasculitis secondary to CTD including RA.

GPA and MPA were defined using the European Medicines Agency algorithm [8]; this provides a standardized method for the application of the ACR (1990) criteria for GPA [9], and the Chapel Hill Consensus Conference definition for GPA and MPA [10].

ANCA status was determined in a routine laboratory using either IIF on human neutrophils or using a commercial ELISA. Patients were deemed to be cANCA/PR3 positive if either IIF or ELISA was positive, similarly for pANCA/MPO. The assays used by the laboratory during the period of the study varied.

Denominator population

The denominator population comprised patients registered with general practitioners in the former Norwich Health Authority [7]. Patients must be registered with a general practitioner in order to access the United Kingdom National Health Service; consequently, virtually the whole population is registered. The denominator adult population (aged >15 years) has increased during the study. The population in 1992 was 413 500 (females 213 500), in 1997 429 000 (females 222 000) and in 2001 444 500 (females 230 500). We estimated the 2008 population (mid-point of the last 5-year period 2005–10), assuming a linear rate of growth of 3.75%, using population growth estimates for the local population obtained from the UK 2001 census [11]. In 2008, the estimated adult population aged >15 years was 459 000 (males 238 000). Age and gender distribution data were available to enable the calculation of age- and gender-specific incidence rates. The population is 97% white Caucasian, which is greater than the average for England of 91%. The population aged >65 years is 20.9%, which is greater than the average for England of 15.9%. Like the rest of England, the population is ageing, with an increasing proportion of inhabitants aged >65 years [11].

Statistical analysis

Age- and gender-specific incidence rates were calculated for each time point using the appropriate corresponding population as the denominator. 95% CIs were calculated using the Poisson distribution for the observed number of cases. The incidence was also calculated using 3-year, centred moving averages. Variability by year was assessed with a chi-squared test. Periodicity was examined for both GPA and MPA using a periodogram. The significance of the observed peak (indicative of a regular periodicity) in the periodogram was assessed using a permutation test for periodicity in short-time series data. This test was developed for microarray data, but it is quite general and can be used in other contexts [12]. In short, this test is based on random orderings of the observed data points in time and the calculation of a periodogram for each of these artificial data sets. The peak seen in the real data is then compared with the peaks seen in the artificial data to see how likely it is to have arisen by chance alone. This approach is robust and makes few assumptions about the data, and does not require a long series of observations. The prevalence was calculated on 31 December 2008. Stata version 10.1 was used for the analysis [13]. Norfolk Research Ethics Committee provided ethical approval for the study.

Results

We identified 111 GPA (58 males) and 58 MPA (32 males) patients who fulfilled the criteria for GPA or MPA from the denominator population. A further 35 patients with possible ANCA AAV were excluded, because they did not fulfill the criteria for GPA or MPA, having either localized ANCA vasculitis, Churg–Strauss syndrome or PAN.

TABLE 1 Incidence of GPA and MPA in Norfolk, UK, 1988–2010

Disease	<i>n</i>	Mean annual incidence (95% CI), per million population, year	Males (<i>n</i>)	Mean annual incidence (95% CI), per million population, year	Females (<i>n</i>)	Mean annual incidence (95% CI), per million population, year
GPA	111	11.3 (9.1, 13.4)	58	12.3 (9.1, 15.7)	53	10.5 (7.6, 13.4)
MPA	58	5.9 (4.4, 7.5)	32	6.8 (4.6, 9.6)	26	5.1 (3.3, 7.5)
Total	169	17.2 (14.7, 20.0)	90	19.1 (15.3, 23.1)	79	15.6 (12.3, 19.4)

Population mid-point of study in 2000 (444 500 total, 214 000 males) was taken as the denominator population.

The average annual incidence of GPA was 11.3/million (95% CI 9.1, 13.4) and for MPA 5.9/million (95% CI 4.4, 7.5) (Table 1). The age distribution showed that the GPA and MPA were most common in those aged 65–74 years (GPA 31.4/million; MPA 20.6/million) (Fig. 1). On 31 December 2008, there were 67 GPA and 29 MPA patients alive, and hence the prevalence of GPA was 145.9 (113.1–186.9)/million and MPA was 63.1 (42.2–90.8)/million.

The peak annual incidence for GPA was in 2005 [28.3/million (95% CI 15.1, 48.4)], with the lowest annual incidence in 2002 [2.2/million (95% CI 0.6, 12.5)] (Fig. 2). In addition, there was an apparent cyclical pattern for GPA, with other peaks occurring in 1990 and 1996 (Fig. 2). The peak incidence for MPA occurred in 2008 [15.2/million (95% CI 6.1, 31.3)] and the lowest incidence was in 1995, when no case of MPA was observed. Rates varied significantly by year for both GPA and MPA ($P=0.01$ and $P<0.001$, respectively, chi-squared test on 22 degrees of freedom). Examination of the periodogram looking for evidence of a non-random pattern showed a peak at the natural frequency of 3/23, corresponding to a period of 7.6 years, ($P=0.017$, using permutation test). There was no evidence of periodicity for MPA ($P=0.85$).

During 2000–10, there were 78 ANCA-positive patients. There were 52 GPA patients of whom 49 (94%) were ANCA positive, and there were 31 MPO patients, of whom 29 (93.5%) were ANCA positive. Analysis of the incidence of cANCA/PR3- or pANCA/MPO-positive vasculitis showed that positivity for ANCA followed the same pattern as GPA and MPA, respectively (Fig. 3).

Discussion

In this study, we describe the results of the longest prospective epidemiological study of GPA and MPA. We have shown for the first time evidence of different patterns of occurrence for GPA and MPA, with GPA occurring in a cyclical pattern. We had noted previously a peak in GPA during 1996–98. As the duration of the study has increased, it has become apparent that a second peak occurred during 2005. The periodicity is ~7.6 years. A peak occurred in 2005 for cANCA/PR3-positive vasculitis but not for pANCA/MPO-positive patients.

Our study shows that the incidence of GPA is relatively high in the UK compared with other populations and appears to be rising with time. The incidence of GPA in other

Fig. 1 Mean incidence of GPA and MPA by age.

white Caucasian populations has been reported to be between 2/million and 12/million using current classification criteria [2, 14]. The most recent study from southern Sweden reported an incidence of 9.8 (7.4–12.2)/million [14]. Our average incidence of 11.8/million is higher than we have previously reported; between 1988 and 1997, we reported an incidence of 9.7/million [7]. Our estimate for MPA is in keeping with other Caucasian populations [2].

The incidence of GPA is higher than that reported from the UK General Practice Database (GPRD), in which the annual incidence was 8.4/million (95% CI 7.5, 9.4) [15]. In the GPRD, MPA is not a separately classified condition and therefore we cannot estimate the occurrence of MPA in that population. The GPRD study was dependent on the physician-given diagnosis. In the analysis of the GPRD data, it was only possible to verify the diagnosis of GPA and not other types of vasculitis. The incidence of GPA may be underestimated in that study, if some cases were erroneously misclassified as other types of vasculitis such as Churg–Strauss syndrome or PAN.

The prevalence of GPA reported in the present study is among the highest reported (reviewed in Ref. [2]), but is consistent with the data from southern Sweden where a prevalence of 160/million was recorded on 1 January 2003 [16]. The prevalence in our own population and the UK has been gradually increasing. In our population on 31 December 1997, the prevalence was 62.9/million,

Fig. 2 Incidence of GPA and MPA. (a) Incidence of GPA and MPA by year; (b) incidence of GPA and MPA plotted as moving 3-year averages.

compared with 148/million at the end of 2010 [7]. The prevalence of MPA has also increased in the UK, although it is currently not as high as that seen in Sweden (94/million). The increasing prevalence is probably due to better survival with modern treatment approaches.

A cyclical pattern of occurrence might be indicative of an infectious aetiology or trigger. While peaks in incidence could occur by chance due to random fluctuations (indeed, there was significant year-to-year variation), our analysis provides evidence of a non-random component to the occurrence of GPA with a period of 7.6 years. In contrast, no non-random component was demonstrable for MPA.

Diagnostic delay tends to be greater for GPA than MPA, as there may be a longer prodromal phase with GPA before systemic disease evolves. The same cyclical pattern of incidence was seen when the incidence was calculated as overlapping 3-year periods; this has the effect of partially correcting for diagnostic delay.

The early rise in incidence could have been due to the introduction of ANCA testing, as was speculated in 1990 [17], but the subsequent decrease in incidence suggests that was not the case. In addition, it would be expected

Fig. 3 Annual incidence of ANCA and disease subtype. (a) Annual incidence of cANCA and GPA; (b) annual incidence of pANCA and MPA.

that MPA would follow a similar pattern to GPA if there was an association with changes in the practice of ANCA testing.

In Scandinavia, a study of patients hospitalized with small-vessel vasculitis and renal involvement demonstrated a cyclical pattern of occurrence during 1975–95 with a 3- to 5-year periodicity [18]. Non-random peaks with periodicity of 3 years were observed for AAV as a group, but not GPA or MPA in a study from northwest Spain [19]. Other studies have reported increases in the incidence of both GPA and MPA, but all have often been of shorter duration than the present study [2, 20]. The GPRD study conducted in the UK between 1990 and 2005 did not show such large variations in the occurrence of GPA in a cyclical pattern [15]. In that study, we did not have access to accurate dates of onset, only of first entry in the database. The GPRD population covers the whole country and is much less stable as general practices have both joined and left the database.

The major strengths of the present study are the length (23 years) and the well-defined population, which has remained stable. There have not been any major rapid influxes or effluxes of population, which could explain the changes observed. The stability of our population together with geographical cohesion means that our results accurately reflect the occurrence of GPA and MPA in a single community.

Classification of a patient into GPA or MPA may be difficult because of the overlapping clinical features. The use of the algorithmic approach standardizes the classification and has been shown to be a reliable method in several different populations [8, 21]. Biases may be unwittingly introduced despite this standardized approach. We therefore looked at the occurrence of two classical types of ANCA, cANCA/PR3 and pANCA/MPO, irrespective of the patient's diagnostic classification. cANCA/PR3 positivity is strongly associated with GPA, whereas pANCA/MPO is associated with MPA, and hence changes in the incidence of cANCA/PR3-positive vasculitis and pANCA/MPO-positive vasculitis should mirror changes in the occurrence of GPA and MPA. We were only able to conduct this analysis for the period 2000–10. The ANCA data set prior to 2000 was incomplete, and specific IIF patterns and PR3/MPO status was not determined before 2000. The pattern of occurrence of cANCA/PR3-positive vasculitis and pANCA/MPO-positive vasculitis mirrored that seen for GPA and MPA, suggesting that there was no classification bias to explain the changing pattern seen for GPA and MPA. We do not believe that changes in the classification of vasculitis explain the patterns observed.

There has been much debate about whether GPA and MPA are the same condition or two separate conditions because of the overlapping clinical features. The data presented here support the idea that GPA and MPA are separate conditions with different risk factors. There is growing epidemiological evidence to support this. GPA is uncommon in some non-Caucasian populations, such as the Japanese, where most ANCA-positive vasculitis can be classified as MPA in association with pANCA/MPO [6]. In Japan, renal AAV is almost exclusively due to MPA [6, 22]. Within Europe, there is evidence that GPA is less common in patients of southern European genetic background, with MPA being perhaps twice as common as GPA [23].

In conclusion, this study supports the idea that GPA and MPA may be distinct conditions with different trigger factors, and the cyclical occurrence supporting the notion that GPA may be triggered by an infection.

Rheumatology key messages

- GPA is approximately twice as common as MPA.
- GPA has a non-random pattern of occurrence, and peaks occur every 7.6 years.
- MPA does not have a cyclical pattern of occurrence.

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