The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations

V. Petursdottir, H. Johansson, E. Nordborg and C. Nordborg

Departments of Clinical Pathology and Rheumatology, Sahlgrenska University Hospital, Göteborg, Sweden

Abstract

Objective. The aim of this work was to study changes in the incidence of biopsy-proven giant cell arteritis (GCA) over a period of 20 yr in Göteborg, Sweden.

Methods. All cases of biopsy-verified GCA between 1976 and 1995 were included in the study. The annual incidence was calculated for the whole material, for women and men separately, and its fluctuations were tested statistically. In addition, the monthly variation during the last 9 yr could be statistically analysed for the whole material.

Results. In total, 665 patients were diagnosed with biopsy-verified GCA during the 20 yr period. The average annual incidence was 22.2/100 000 inhabitants over 50 yr of age (women 29.8, men 12.5). The annual incidence increased significantly with time (P < 0.001) for both men and women. Statistical analysis did not reveal any cyclic fluctuation in the annual incidence (P = 0.26), while the monthly number of positive biopsies showed significant fluctuation with peaks in late winter and autumn (P = 0.041).

Conclusions. The annual incidence of biopsy-positive GCA increased during the years 1976 through 1995. The significant seasonal variation, as well as considerable variation in annual incidence, might be due to the influence of exogenous triggering factors, such as infections. Further support for an exogenous aetiology, in terms of a statistically significant cyclic fluctuation of the annual incidence, was not found, however.

Key words: Giant cell arteritis, Epidemiology, Incidence, Infections, Periodicity.

The aetiology and pathogenesis of giant cell arteritis (GCA) are incompletely understood. Previous immunological, morphological and epidemiological reports indicate that it is multifactorial. HLA-DR4 predominance and a local activation of T lymphocytes in the lesion [1] suggest an antigen-driven disease. Weyand et al. [2] showed that a small proportion of the T cells show clonal expansion of the same subtype in separately located inflamed arterial segments in the same artery, which further supports the antigen hypothesis. The possible antigen might be autologous, but it may also be of external origin. Significant media atrophy and calcifications have been shown in non-inflamed arterial segments in GCA when compared with age- and sex-matched controls. Previous light and electron microscopic studies have indicated that the inflammation starts as a focal foreign body giant cell reaction to calcification in the arterial wall [3]. Arterial degeneration might thus be one prerequisite for the occurrence of GCA. Genetic factors seem to be of importance. There is a predominance of certain variants of HLA-DR4 allele expression in patients with GCA [4, 5]. The known incidence of biopsy-proven GCA is greatest in populations in Scandinavian countries [6–10] and in communities with a strong Scandinavian ethnic background [11, 12]. The incidence is lower in southern Europe [13, 14] and Israel [15, 16], very low in the White population in the southern USA, and GCA is rarely seen in Blacks [17, 18].

Although there is no proof that GCA is an infectious vasculitis, the role of infectious agents in its pathogenesis has been repeatedly suggested [12, 19–27]. Rhythmic fluctuation in disease incidence suggests an exogenous aetiopathological factor like recurring epidemic infections. The aim of the present study was to analyse the incidence of biopsy-positive GCA in Göteborg, Sweden, for a period of 20 yr with special reference to cyclic variation.

Patients and methods

The sources of information about the temporal artery biopsies were the files of the Department of Pathology, Sahlgrenska University Hospital, which is the referral centre for clinical histopathology in Göteborg. The biopsies were taken at four referring clinics in Göteborg; referring clinics outside Göteborg were not included. During 1993–1995, a minority of the biopsies (165 of 872) were referred to a private laboratory outside Göteborg (Medilab, Malmö). These arteries were also

Submitted 1 December 1998; revised version accepted 21 June 1999.

Correspondence to: V. Petursdottir, Department of Clinical Pathology, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden.
The investigation comprised all positive and negative temporal artery biopsies in Göteborg during the period 1 January 1976 through 31 December 1995. Owing to the retrospective, morphology-based nature of this study, patients with only a clinical diagnosis of GCA, in whom a temporal artery biopsy was not performed, were not included. Our data of incidence should thus be regarded as minimum values. Recommended criteria for temporal artery biopsy in Göteborg throughout the investigated period were polymyalgic symptoms and/or temporal–cranial symptoms + an increased sedimentation rate + age above 50 yr and no signs of rheumatic disease other than GCA. Alternative criteria were general symptoms of disease + increased sedimentation rate where no other cause was found. The general policy in Göteborg is to perform the biopsy before steroid therapy. If this is not possible, the biopsy is generally taken shortly thereafter. There is ample evidence in the literature that the inflammatory reaction remains for a long time after the initiation of high-dose steroid therapy [28–30].

The biopsies taken in Göteborg are unilateral with very few exceptions. Serial biopsies are not, and have not been, performed in Göteborg, and a second biopsy is uncommon. The indication for a second biopsy is generally a negative first biopsy. The results have thus not been influenced by double or multiple positive biopsies. We have no complete information as to the length of the 4971 biopsies included in this retrospective study. According to scattered samples, there has been no significant change in length over the years.

Every biopsy report was checked; the slides were re-examined in the case of an inconclusive statement. To receive the diagnosis of GCA, the biopsy had to show signs of arteritis with a mononuclear cell infiltrate in the arterial wall with or without the admixture of giant cells.

The incidence of biopsy-positive GCA and its yearly variation for men, women and in total was assessed and analysed statistically (see below). For the last 9 yr (1987–1995), we were able to assess the biopsy number for each month and analyse its fluctuations. Some data concerning the period from 1977 to 1986 have previously been reported by our own group, although no analyses of the periodicity were performed [10].

Göteborg is the second largest city in Sweden. Its population is predominantly Caucasian, with an average of 433 337 inhabitants (range 424 085–449 189) during the studied 20 yr period. The number of both men and women over 50 yr of age decreased slightly during the period (women: 86 048 to 81 403; men: 69 954 to 64 749) [31].

**Statistical methods**

A Poisson model [32] was used to study the relationship between calendar year and the risk of GCA. The hazard function of individuals older than 50 yr was assumed to be \( \exp[\beta_0 + \beta_1 \times (\text{calendar year} - 1975) + \beta_2 \times \text{calendar year}] \).
The expected and observed numbers of biopsy-positive GCA in Göteborg during the period 1976–1995 for women, men and both sexes. 

A simpler variant of this model ($\beta_2 = 0$) was applied for men. The coefficients $\beta_1$ and $\beta_2$ reflected trends of the risk; $\beta_1 = \beta_2 = 0$ corresponded to no change of risk. Using those results, which were based on demographic data, the expected number of GCA was calculated for each year. Furthermore, the $\chi^2$ statistic:

$$\sum_{j=1976}^{1995} \frac{(\text{observed} - \text{expected})^2}{\text{expected}} (1)$$

was used in order to assess whether there was a non-random (e.g. cyclic) variation with time.

In order to assess a possible variation with month, the following model was used: hazard function $= \exp [\beta_0 + \beta_1 \cdot (\text{calendar year} - 1975) + \beta_2 \cdot \text{sex} + \beta_3 \cdot \text{month}]$, where month was the order number of the month. A statistic test of type (1) above, but with $j=1–12$, was used. The test for trend in contingency tables [33] was used to test whether the probability of a positive outcome changed with time.

Two-tailed tests were used.

Results

The number of temporal artery biopsies examined during the period was 4971. A total of 13.4\% ($n=665$) was positive for GCA. Of these, 664 patients were older than 50 yr. Only one male patient was aged 49 yr. The average annual incidence for the entire population was 7.7/100 000 inhabitants and 22.2/100 000 for the population over 50 yr of age (women 29.8, men 12.5) (Table 1).

The annual incidence of biopsy-positive GCA in the population over 50 yr of age increased significantly ($P < 0.001$) for both men and women between 1976 and 1995. The estimated yearly increase in incidence was 5.2\% for men (95\% CI 2.4, 8.1), 13.9\% for women (1.06, 22.3) and 10.9\% in total (4.4, 17.9).

The annual incidence of biopsy-positive GCA per 100 000 persons over 50 yr of age varied from 4.3 to 26.9 for men and from 11.6 to 49.3 for women (Table 1). However, statistical analysis did not reveal any cyclic fluctuation in the number of cases of biopsy-proven GCA for men ($P > 0.30$), women ($P > 0.30$) or the total material ($P = 0.26$), i.e. the observed annual fluctuations were random (Table 1, Fig. 1).

Assessment of the monthly number of positive biopsies showed statistically significant fluctuations ($P = 0.041$), with peaks in late winter and autumn (Fig. 2).

Like the positive biopsy incidence, the total biopsy rate increased during the period. However, the number of positive biopsies per 100 biopsies did not change significantly ($P = 0.07$) (Table 1).

Discussion

Our results are consistent with several previous investigations showing that the incidence of GCA is increasing with time [10, 12, 34]. In Göteborg, Bengtsson and Malmvall [7] found the average annual incidence of biopsy-proven GCA to be 16.8/100 000 inhabitants over 50 yr during the period 1973–1975. Nordborg and Bengtsson [10] reported an average incidence of 18.6 during the period 1977–1986, while it was 22.2 in the present study (1976–1995). The increased number of biopsy-positive cases observed with time, and the constant relationship between positive and negative biopsies which we found, could be due to a true increase in
incidence, but it could also be influenced by the awareness of the disease among clinicians.

So far, no statistically significant rhythmic pattern has been found regarding the annual incidence of GCA. The observed variation in annual incidence among 664 cases of biopsy-proven GCA older than 50 yr in the present study proved not to be cyclic, but random. The Mayo Clinic group presented rhythmic fluctuations in the incidence of GCA with peaks every seventh year, which did not reach statistical significance, however [12]. The Olmstead County material spanned over 42 yr and included 125 cases, 115 of which were biopsy proven. Elling et al. [21] found some fluctuation in Danish materials which differed in periodicity from the Olmstead County material.

In the present study, we found a significant fluctuation in monthly incidence of biopsy-positive GCA, with peaks in late winter and autumn. This is in contrast to Kinmont and McCallum [35], who found the greatest incidence of GCA in the summer in England, as did Sonnenblick et al. [16] for biopsy-proven GCA in Jerusalem, Israel. Jonasson et al. [36] found an incidence peak in January and May in Scotland. One reason for differences between the studies may be that whereas the present investigation focuses on the day of biopsy, the other authors based their statistics on the start of symptoms. Seasonal variations may indicate a role of infections or other exogenous factors in the pathogenesis of GCA. However, the pattern might be confused by other factors independent of the aetiology and pathogenesis of GCA, such as seasonal variations in clinical activity as well as patients’ delay.

Since fever, elevated sedimentation rate and generalized illness are some of the clinical symptoms in GCA, an infectious process has repeatedly been suggested. Cimmino et al. [20] found an increased prevalence of antibodies to adenovirus and respiratory syncytial virus in serum from patients with polymyalgia rheumatica compared with controls, while Duhaut et al. [37] found an increased prevalence of serum IgM to parainfluenza virus type 1 in patients with polymyalgia rheumatica and temporal arteritis compared with controls. Fest et al. [22] used the in situ hybridization technique to detect cytomegalovirus DNA in temporal artery biopsies and found a significantly higher presence in patients with GCA than in patients with polymyalgia rheumatica and other control groups. In a recent study [23], immunocytochemistry and polymerase chain reaction did not reveal varicella–zoster infection in inflamed temporal artery biopsies. A few cases associated with parvovirus B19 [26] and Borrelia infection have been reported [19, 24, 27]. Bacon et al. [38] found hepatitis B virus (HBV) antibodies in polymyalgia rheumatica patients, while later studies did not confirm this observation [39–41]. Russo et al. [25] strongly suggested a correlation between different infections and the onset of GCA in a clinical retrospective study. Thus, although GCA has not been shown to be a truly infectious vasculitis, associated with a specific agent, it may be speculated that various infections might act as triggers by activating the immune system in genetically susceptible patients with certain predisposing lesions in their arterial walls.

In summary, in the present study we found an increase in the annual incidence of biopsy-positive GCA during the years 1976 through 1995. The significant seasonal variation as well as a considerable variation in annual incidence could, theoretically, be due to the influence of exogenous factors such as infections. Further support for an exogenous aetiology in terms of a statistically significant cyclic fluctuation of the annual incidence was not found, however.

Acknowledgements

The skilled technical assistance of Margareta Persson and Fariba Moraghebi is gratefully acknowledged. This study was supported by grants from the Göteborg Medical Society, the Swedish Heart-Lung Foundation, the Swedish Rheumatism Association, Rune och Ulla Amlöfs Stiftelse and Syskonen Holmströms Donationsfond.

References


