Epidemiology of giant-cell arteritis

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Although a case of giant-cell arteritis (GCA) was clearly described by Hutchinson[1] in the late 1880s, it was not until the description by Horton and co-workers[2,3] in the 1930s that this vasculitis came to the attention of most physicians. After their reports, GCA was still considered an uncommon illness. The spectrum of clinical findings associated with GCA, including visual loss, occlusive changes in the large branches of the proximal thoracic aorta, and musculoskeletal symptoms, were described over the following years in case reports and small series. In more recent years, particularly over the last twenty-five years, GCA has become recognized as one of the most common forms of vasculitis, especially in individuals over the age of 60 years. In addition, polymyalgia rheumatica (PMR), a syndrome linked to GCA and characterized by proximal aching and stiffness, is even more common.[4] Thus, in many populations in the US and Europe, these two conditions are among the most frequent new inflammatory rheumatic diseases that develop in older persons.

GEOGRAPHIC LOCATION AND ETHNICITY

A number of population studies have been carried out determining the incidence rates of GCA in various geographic regions. The results of several selected recent investigations are listed in **Table 1**. The highest incidence rates observed have been reported from Norway. Workers from two neighboring southern Norwegian centers studied the incidence of GCA during time ranges that overlapped. Haugeberg and co-workers[5] searched clinical and biopsy databases to determine the incidence of GCA over a 5-year period, 1992 to 1996, in the population of Vest Agder County, Norway. Fifty-three cases of GCA were diagnosed over this period, 94% of which were biopsy positive. This provided an average annual incidence over the study period of 32.8 cases per year in persons over age 50 years. Gran and Mykelbust[6] asked all physicians in Aust Agder County to refer all patients suspected of having GCA and PMR to the Department of Rheumatology where they worked. They also evaluated suspected cases admitted to other hospital departments. Sixty-six cases of biopsy-verified GCA were identified between 1987 and 1994. These cases produced an annual incidence rate over this time of 29.0 cases per year in persons aged 50 years and older.

TABLE 1
GIANT-CELL ARTERITIS: SELECTED ANNUAL INCIDENCE RATES

Location of Study	Years Included in the Study	Average Annual Incidence Rates*
Norway[5]	1992-1996	32.8
Norway[6]	1987-1994	29.0
Iceland[7]	1984-1990	27
Sweden[8]	1976-1995	22.2
Denmark[9]	1982-1994	20.4
Finland[10]	1984-1988	20.7
Finland[11]	1969-1989	6.9
Olmsted Cty, USA[18]	1950-1999	19.0
Spain[12]	1981-1998	10.2
Israel[13]	1980-1991	10.2
Italy[14]	1980-1988	6.9

*Per 100,000 population aged 50 years and older.

The rates in Iceland have been found to be at a similar level. Baldursson and colleagues[7] ascertained cases by a search of all hospitals in Iceland and a review of all temporal artery biopsies during a seven-year period, 1984 to 1990. The authors identified 133 patients with GCA. The average incidence rate of GCA over this 7-year period was 27/100,000. Petursdottir et al[8] identified all cases of biopsy-verified GCA between 1976 and 1995 in Goteborg, Sweden. Six hundred sixty-five patients had been diagnosed with GCA over this 20-year period. The average annual incidence rate was 22.2 per 100,000 inhabitants over 50 years of age. Elling and co-workers[9] determined the number of patients with GCA between 1982 and 1994 in two regions of Denmark, using national patient registry data. Over this period the average incidence rate was 20.4 new cases each year in persons over 50 years of age.

Two studies from Finland have shown large differences in incidence rates. In one from Western Nyland, reported by Franzen, Sutinen, and von Knorring,[10] 16 patients with biopsy-positive GCA were diagnosed over five years,

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1984-1988, in a population of 44,500 persons. The average incidence rate over the first 44 months of the study period, calculated retrospectively, was 20.7 per year in persons in the population over age 50 years. A 16-month prospective part of the study yielded an increased rate of approximately 28 cases per year per 100,000 persons over age 50 years. The second study, by Rajala and co-workers,[11] was from Tampere, in south central Finland. During the 20-year period from 1969 to 1989, 66 patients with histologically verified GCA were identified. The annual incidence of GCA in persons 50 or older was 4.5 over the period from 1970 to 1979 and 9.2 in the period from 1980 to 1989. The reason for the difference in rates between the two Finnish studies is unknown. The investigation by Franzen et al[10] was performed in a population nearer Sweden and may have contained persons with Swedish ethnicity, whereas those in Tampere may be of different ethnicity.

Population surveys from Mediterranean countries have shown lower incidence rates of GCA. In a recent study by Gonzalez-Gay et al[12] from a region in northwest Spain with a population of approximately 250,000 persons, 161 patients with GCA were diagnosed over 18 years between 1981 and 1998. The average annual incidence rate per 100,000 persons over age 50 was 10.2. In Israel, Sonnenblick and others[13] found 84 patients with GCA in Jerusalem over a 12-year period. The annual incidence rate for this population was also 10.2 per 100,000 persons aged over 50 years. The incidence rate was similar among non-western and western Jews. In northern Italy, Salvarani and colleagues[14] found an incidence rate of 6.9 per 100,000 persons aged 50 and older over a 9-year period.

In the US, incidence studies have been done mainly in Olmsted County, MN, a region in the northern part of the country which has an ethnic background similar to that of mid and northern Europe.[15-17] In a recent as-yet unpublished updated series from the Mayo Clinic, 175 cases of GCA were identified between 1950 and 1999. This produced an average annual incidence of 19.0 per 100,000 in persons 50 years and older.[18] One other center in the US performed a population survey of GCA a number of years ago. Smith and co-workers[19] surveyed the population of Shelby County, Tennessee, for the years 1971 to 1980. Shelby County is in a south central location along the Mississippi River. The average annual incidence was only 1.58 for those over age 50. The incidence was 7 times greater in whites than in blacks. Clinical features in the patients with GCA were similar to those of other populations. The difference from results found in Minnesota could be accounted for only in part by racial distributions. Similar studies in other southern geographic areas are needed to place these latter findings in perspective, but have yet to be done.

In summary, the frequency of GCA in northern Europe has been well documented. There appears to be a decreasing incidence of GCA from northern to more southern countries. This gradient may also be present in the US but has been less well studied. Rates in most Scandinavian countries and in Minnesota, a population of similar ethnic background, are approximately 20 or more per 100,000 persons over the age of 50 years, and those in other parts of Europe are approximately 10 or less.

The different results in the two studies from Finland are intriguing. The different findings could be due to ascertainment or other factors. Rates found by Rajala and co-workers[11] were higher in the second half of the study period. Alternatively, the differences may reflect ethnic variations in different regions of Finland, the higher rates being found in those with a genetic make-up more representative of Sweden, Finland's next-door neighbor, and the lower rates measuring another native ethnic group with genetic characteristics of other central and southern European countries. Incidence rates of GCA in African and Asian countries have not been studied thoroughly, but from information available, the frequency of GCA in these populations appears to be much less than in Caucasians. Reports have shown a relationship between HLA-DR4 and GCA and PMR.[20] HLA types vary in different ethnic groups and HLA-DR4 is less common in Mediterranean and other populations with a low incidence of GCA. Because of the inflammatory nature of GCA and PMR, immunogenetic factors may be important in susceptibility of these conditions. However, it is not known if the varying incidence rates discussed above are related to immunogenic markers. As far as can be determined, clinical features of GCA are similar in the various locations with different incidence rates.

■ YEARLY/SEASONAL VARIATIONS

Nearly all studies have found women to be affected more commonly than men, in a ratio of about 3 to 2. The survey in Spain is the exception where men were noted to be more numerous.[12] Essentially, all surveys that have evaluated incidence over time have shown an increase in the rates over years. However, changes of incidence of PMR, which is linked to GCA, have been less clear. In Olmsted County, the incidence of PMR has varied from year to year but has remained relatively stable over the past three decades.[21] This is surprising in view of the nearly uniform finding of increase in the incidence of GCA and the close link between GCA and PMR. PMR is a less well-defined syndrome in that it has no definitive diagnostic test such as temporal artery biopsy in GCA. It is also possible, for example, that PMR is caused or precipitated by several factors, or may be several disease entities which cannot be separated by clinicians at this time.

In the investigation of GCA in Olmsted County, MN, in addition to an increase in incidence rates over the study period, a cyclic pattern was observed, with peaks every 5 to 7 years **(Figure 1)**. This suggested that an environmental factor(s) might be involved in precipitating the disease.[17] Subsequent to this observation, Gabriel and co-workers[22] prospectively examined temporal artery biopsy tissue from 50 consecutive patients presenting for temporal artery biopsies for the presence of B19 DNA, using the polymerase chain reaction. Amplicons for human beta-globulin, but not for cytomegalovirus, were

produced for all tissue samples. A statistically significant association between histologic evidence of GCA and the presence of B19 DNA in temporal artery tissue was found (P=0.0013). The PCR results for B19 agreed in 29 of 30 samples tested by a second laboratory, the Centers for Disease Control, Atlanta, GA. The finding of B19 in the temporal artery wall in patients with GCA suggested that B19 may play a role in its pathogenesis. Further studies on this virus are needed to fully understand the significance of these results.

Other workers have also noted variations in the incidence of GCA, along with additional evidence of infections or another environmental factor(s) in the development of GCA. Elling, Olsson, and Elling[9] prospectively recorded the incidence rates of GCA and PMR in 13 of 16 counties in Denmark between 1982 and 1993. Pronounced quarterly and annual variations of the incidence of GCA and PMR were found in each of the counties. Cyclic fluctuations were seen simultaneously in several regions irrespective of the incidence rates, with a clustering in five peaks. Distinct peak rates of GCA and PMR occurred in close association with two epidemics of *Mycoplasma pneumoniae* infection. Two incidence peaks were seen, partly related to two epidemics of parvovirus B19 and to one epidemic of *Chlamydia pneumoniae*. The synchronous variations in the incidences of GCA and PMR in the several regions and close concurrence with epidemics of viral infections suggested that GCA and PMR may be triggered by certain viruses or other agents. Petursdottir and colleagues[8] from Goteborg, Sweden, studied changes in incidence of GCA in their population over 20 years. As did others, they noted an increase in rates over the period (P<0.001) and a variability of monthly rates with peaks in late winter and autumn (P=0.04). However, no cyclic occurrence was observed.

URBAN/RURAL INCIDENCE

Two investigations have found higher incidence rates in locations of high population density. This was noted the Danish study above[9] and in a report from Germany.[23] In the latter, Reinhold-Keller and colleagues investigated the prevalence of primary systemic vasculitis in northern and southern Germany. Each catchment area included both urban and rural areas. GCA was the most frequent type of vasculitis found. GCA was also significantly more prevalent in urban than in rural populations. Although a lower ascertainment of GCA in rural regions was not excluded as a cause of the differences, the authors considered it possible that environmental factors may be involved in the development of GCA and should be looked for in future studies.

ASSOCIATIONS WITH INFECTIONS

In addition to the study by Gabriel and coworkers noted above,[22] other investigators have looked for an infectious link to GCA. Duhaut and co-workers[24] performed serologic tests on 350 new patients with GCA or PMR for viruses known to induce multinucleated giant cells in human pathology. These included the parainfluenza viruses, respiratory syncytial virus, measles virus, herpesviruses type 1 and 2, and the Epstein-Barr virus. Positive serologic titers for IgM antibodies against parainfluenza viruses were found in 38% of cases versus 20.9% of controls (P=0.00005). The association was even stronger in the positive-biopsy GCA group. In these patients, 43.3% had positive titers. Only parainfluenza type 1 was associated with GCA regardless of the season or the geographic origin of the cases. Positive rates for all other viruses tested were similar in both cases and controls. The authors concluded that findings indicated that reinfection with parainfluenza type 1 may be associated with the onset of GCA, especially biopsy-positive cases.

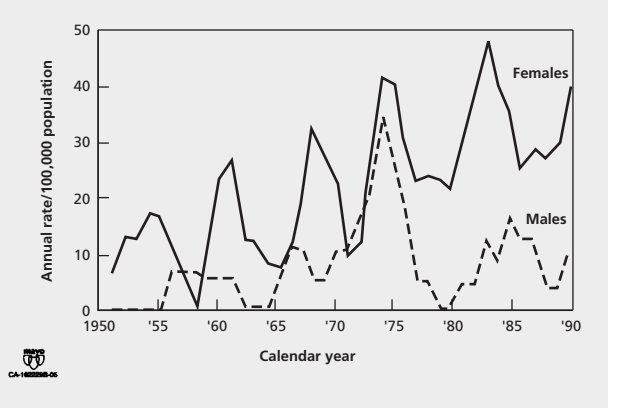

Figure 1. Incidence of giant-cell arteritis in Olmsted County, MN, 1950-1990. Three-year moving average method was used to develop curves. Peak incidence rates appear to occur in females every 5 to 7 years. Data from reference 27.

OUTCOME

The course of GCA is variable, with frequent relapses,[11] but most patients are able to discontinue prednisone after one to two years without recurrence of symptoms, indicating a gradual resolution of vascular inflammation in most patients.[25] Vascular complications, however, may result in the patient's death.[11,26-28] These include strokes due to occlusions of one or more large arteries in the cervical region and rupture of the thoracic aorta as a result of arteritic involvement. In addition, therapy for GCA, especially long-term use of glucocorticoids, is frequently associated with adverse events, such as infections, or hip fractures that may cause disability in older persons. These adverse events related to treatment may contribute importantly to the patient's ultimate outcome.[29] In spite of these events in some patients, the majority of long-term survival studies have shown no excess mortality.[17,30-31] No reliable predictors at the time for disease severity or duration, development of aortic aneurysms, or death have been identified. Hachulla and co-workers[32] found that long-term survival was better in those without initial ocular manifestations and those who were on less than 10 mg of prednisone per day at the end of 6 months of therapy.

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