Epidemiology and Genetics

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Abstract

Giant cell arteritis (GCA) is the most frequent primary systemic vasculitis among patients ≥50 years of age, peaking in the seventh and eighth decade of life. The annual incidence rate of GCA increases with advancing age up to a maximum in the 70–79 year age group and then decreases slowly. Women are more affected than males with 3:1 ratio. The highest incidence is reported in North European countries and in North American population of the same descent with an incidence that varies between 32.4/100,000 people, older than 50 years of age in Norway and 18.9/100,000 people in Olsted County, Minnesota, USA Prevalence in GCA follows the same latitude distribution of incidence with higher prevalence in the Northern hemisphere compared to the Southern Europe and non-European country.

Prevalence study from Mayo Clinic reported that prevalence rate of GCA between 1950 and 2009 among women was 304 (95% CI 229–375) and among men was 91 (95% CI 46–156) per 100,000 population older than 50 years of age.

Compared with general population, all cause SMR (standardized mortality ratio) was not increased in GCA patients (SMR 1.081, 95% CI 0.963–1.214, p = 0.184) and the stratification by regions showed no significant increase in all cause SMR in Europe and the USA. Sex-specific meta-analysis provided by four out of eight studies included revealed the pooled SMR for women was 1.046 (95% CI 0.834–1.314, p = 0.696) and for men was 1.051 (95% CI 0.974–1.133, p = 0.204).

Female sex is the most important genetic risk factors for GCA as reported above.

Polymorphisms of the HLA II gene in particular the presence of HLA DRB1*04 alleles (both HLA DRB1*0401 and HLA DRB1*0404) are systematically associated with GCA supporting the thesis that GCA is driven by an antigen-based immune response.

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Keywords

Incidence · Mortality · Prevalence

2.1 Epidemiology

Giant cell arteritis (GCA) is the most frequent primary systemic vasculitis among patients ≥50 years of age [1], peaking in the seventh and eighth decade of life [2, 3]. In Northwestern Spain infact, the annual **incidence** rate of GCA increased with advancing age up to a maximum in the 70–79 year age group and then decreased slowly [4]. Similar results were obtained in the Olmsted County Minnesota USA population-based study, where the annual incidence increased with advanging age, in the 50–59 age groups was 0.6/100,000 population, while in the over 80 age group the annual incidence was 73.9/100,000 [5]. GCA mainly affects white individuals [6], and it is more common in women than in men [7] with a lifetime risk for GCA of 1.0% in female sex and 0.5% in males [1]. In north European countries, 3:1 ratio of women to men was detected [8, 9], comparable results were observed in the Olmsted County, Minnesota, USA, among 74 patients diagnosed between 2000 and 2009, 80% were women and 20% were men [5].

A lower female male ratio was observed in Israel and in Southern Europe [10, 11].

The incidence of GCA has ranged widely across the world depending on the characteristics of population. In Japan, the reported GCA incidence was 1.7/100,000 [12] while in Gothenburg, Sweden reached 22 per 100,000 [13].

In Olmsted County, Minnesota, USA composed by a predominant white population with northern European ancestry, the incidence of GCA is 19.8% per 100,000 [5]. Few case reports and case series demonstrated that GCA can affect people of any racial background such as Indians, Chinese, African, and Latins but the epidemiological data in these areas are insufficient and incidence/prevalence studies are required to a more accurate project of potential global burden of GCA [14]. The most recent epidemiologic studies are from Italy, Norway, and the UK [15–17]. Table 2.1 summarizes the annual incidence of GCA in the different regions of the world.

Most of the studies on GCA published in the last 30 years support the clue of an increase evidence of GCA with **latitude** in the North hemisphere [3]. As Table 2.1 shows the highest incidence is reported in North European countries and in North American population of the same descent with an incidence that varies between 32.4/100,000 people, older than 50 years of age in Norway [18] and 18.9/100,000 people in Olsted County, Minnesota, USA [2]. The incidence is markedly reduced in the Mediterranean countries and in the Southern Europe with an annual incidence that varies between 12.9/100,000 people in Spain [4] and 1.1/100,000 people in Turkey [29]. A lower incidence is reported among black people from Tennessee [30] with an incidence of 0.4/100,000. Similar results were reported in Japan [12].

Table 2.1 Incidence rates for giant cell arteritis

Study, year	Country (Region/city)	Method of diagnosis	Study period	Population incidence >50 years of age (per 100,000 people/year)
Haugeberg et al. (2003) [18]	Norway (North and West)	ACR criteria	1992–1996	32.4
Baldursson et al. (1994) [19]	Iceland (Nationwide)	ACR criteria	1984–1990	27.0
Boesen et al. (1987) [8]	Denmark (Danish county)	Biopsy proven Clinical GCA	1982–1985	23.3
Nordborg et al. (2003) [20]	Sweden (Gothenborg)	Biopsy proven	1976–1995	22.2
Smeeth et al. (2006) [17]	UK (Nationwide)	Clinical criteria	1990–2001	22.0[a]
Elling et al. (1996) [21]	Denmark (Nationwide)	Biopsy proven	1982–1994	20.4
Kermani et al. (2010) [2]	USA (Minnesota)	ACR criteria	2000–2004	18.9
Salvarani et al. (2004) [22]	USA (Minnesota)	ACR criteria	1950–1999	18.8
Brekke et al. (2017) [16]	Norway (West)	ACR criteria	1972–2012	16.7
Gonzalez Gay et al. (2007) [4]	Spain (Lugo)	Biopsy proven	2001–2005	12.9
Abdul-Rahman et al. (2011) [23]	New-Zealand (Otago)	Biopsy proven	1996–2005	12.7
Bas-Lando et al. (2007) [10]	Israel (Jerusalem)	Biopsy proven or ACR criteria	1980–2004	11.3
Ramsted and Patel (2007) [24]	Canada (Saskatoon)	Biopsy proven	1998–2003	9.4
Barrier et al. (1982) [25]	France (Loire-Atlantique)	Biopsy proven or clinical features	1970–1979	9.4[b]
Pucelj et al. (2018) [26]	Slovenia (Ljubljana)	Biopsy proven or ACR criteria or TA CDS	2012–2017	8.7
Salvarani et al. (1991) [27]	Italy (Reggio Emilia)	Biopsy proven or clinical features	1980–1988	6.9
Salvarani et al. (2017) [15]	Italy (North)	Biopsy proven	1986–2012	5.8
Dunstan et al. (2014) [28]	Australia (South)	Biopsy proven	1992–2011	3.2
Pamuk et al. (2009) [29]	Turkey (Northwest)	ACR criteria	2002–2008	1.1

[a]Reported for people over 40 years

[b]Reported for people over 55 years. *ACR* American college of Rheumatology, *TA CDS* temporal artery color Doppler ultrasonography

Several epidemiologic studies reported a progressive increase in incidence of this vasculitis in particular between 1950 and 1980/1990 [4, 11, 24, 31] but more recent reports from Israel and Olmsted County, Minnesota reported the incident rates leveled off and remained steady with minimal fluctuations through 2009 [31, 32].

Fewer are the **prevalence** studies on GCA. Table 2.2 summarized these data from different regions of the world. Prevalence in GCA follows the same latitude distribution of incidence with higher prevalence in the Northern hemisphere compared to the Southern Europe and non-European country. Prevalence study from Mayo Clinic [31] reported that prevalence rate of GCA between 1950 and 2009 among women was 304 (95% CI 229–375) and among men was 91 (95% CI 46–156) per 100,000 population older than 50 years of age. The prevalence rate increased precipitously from age 50–54 to age 90 in both sexes. Moreover, the authors reported that prevalence estimates remained stable over the long period of observation.

Differences in prevalence and incidence reports in these cohorts are most likely related to differences in disease classification and diagnostic criteria, temporal artery biopsy evaluation, as well as genetic and geographic factors.

The population **health burden** of these disease among older people continued to be substantial. The incident GCA cases will increase secondary to an aging population, therfore in projected worldwide disease burden study on GCA was found that by 2050 more than three million people will have been diagnosed with GCA in Europe, North America, and Oceania [14]. If current treatment will not change, over 140,000 patients with GCA in the USA will come up with acute visual symptoms and receive hospital admission for appropriate treatment with consequent important economic impact con sanitary cost. By 2050, in the USA, US$1.3 billion is expected to have been spent on inpatient management of visual impairment-associated GCA. Moreover, since oral and intravenous corticosteroids still remain the cornerstone of GCA treatment, the treatment side effects should be considered in the long-term management of these patients. By 2050, in the USA, around 360,000 patients with GCA are expected to develop a steroid-induced fractures, a total amount of money to manage this side effect is more than US$6.58 billion.

Several studies have addressed the issue about **mortality** in patients with GCA. However, the conclusions are inconsistent due to the small number of studies, their small sample sizes, and the clinical heterogeneity. A recent meta-analysis combined the published data of all cause, sex-specific, region-specific, and cause-specific standardized mortality ratios (SMRs) in patients with GCA [39]. Eight studies were included and seven analyzed all-cause mortality. Compared with general population, all cause SMR was not increased in GCA patients (SMR 1.081, 95% CI 0.963–1.214, $p = 0.184$) and the stratification by regions showed no significant increase in all cause SMR in Europe and the USA. Sex-specific meta-analysis provided by four out of eight studies included revealed the pooled SMR for women was 1.046 (95% CI 0.834–1.314, $p = 0.696$) and for men was 1.051 (95% CI 0.974–1.133, $p = 0.204$); therefore, no sex-specific significant differences in SMR were demonstrated. In contrast, the risk of mortality of cardiovascular disease was significantly increased with an SMR of 1.312 (95% CI 1.136–1.516, $p < 0.001$).

Table 2.2 Prevalence studies on GCA

Study, year	Country	Age, years	Method of diagnosis	GCA prevalence rate per 100,000 (95% CI)		
				Overall	Female	Male
Crowson CS et al. 2015 [31]	USA	≥50	ACR1990	204 (161,254)	304 (229.375)	91 (46,156)
Catanoso M et al. 2012 [15]	Italy	≥50	Positive TAB, ACR1990	87.9 (75.8,101.4)		
Lawrence RC 2000 [33]	USA	≥50	ACR1990	228 (192,268)	344	200
Yates M et al. 2013 [34]	UK	≥55	ACR1990	250 (110,390)	330 (120,550)	160 (0–320)
Kobayashi S et al. 1997 [12]	Japan	≥50	ACR1990	1.5		
Gonzalez Gay MA et al. (1991) [35]	Spain	≥50	Hunder	60		
Herlyn K et al. 2006–1994 [36]	Germany	≥50	ACR1990	44 (2004) (39.9,48.1) 24(1996) (1.64,31.5)	61.2 (54.4,66.0)	21.9 (19.0,25.)
Pamuk ON et al. [29]	Turkey	≥50	ACR1990	20 (16,24)		
Adrianakos A et al. 1996 [37]	Greece	≥50	ACR1990	80 (10,150)		
Mohammad A et al. 2011 [38]	Sweden	≥50	Positive TAB	110 (100,120)		

ACR American College of Rheumatology, *GCA* giant cell arteritis, *TAB* temporal artery biopsy

Chazal and colleagues [40] using the death certificates compiled by French Epidemiological Centre on Medical Causes of Death for the period 2005 and 2014 reported the mean age of death was 86 (±6.8) years and the overall age of SMR among GCA patients was 7.2 per million people. Throughtout the study period, the mean age of death was significantly increased ($r = 0.17$, $p < 0.0001$). The most frequent associated diseases were cardiovascular (79%) and infectious (35%).

From the same French death certificate database between 1980 and 2011 Aouba and colleagues [41] reported the annual SMR for GCA increased to a peak in 1997 then decreased in the following years (Spearman's correlation test, both $P < 0.0001$). GCA deaths were frequently associated with aortic aneurysm and dissection (1.85% of death certificates), hypertensive disease (20.78% of death certificates), diabetes mellitus (11.27% of death certificates), ischemic disease (16.54% of death certificates), and infectious and parasitic disease (12.12% of death certificates).

UK-based Clinical Practice Research Datalink between 1990 and 2014 was used to identify 9778 newly diagnosed GCA patients [42]. Cases were matched to non-vasculitic patients on age, sex, practice, and years of history before cohort entry. GCA patients compared with controls had increased mortality during the first year following the diagnosis (adjusted HR = 1.51, 95% CI 1.40–1.64) and slighlty increased mortality during the period of 1–5 years after the diagnosis (adjusted HR = 1.06, 95% CI 1.00–1.12). The mortality risk differed by age with a greater increased 1-year mortality in those with a diagnosis at an age less than 65 years, but not by sex or calendar year of the cohort [42].

Survival predictors in giant cell arteritis were evaluated in a recent Italian study [43]. Polymyalgia rheumatica (PMR) at diagnosis and the inflammation limited to the adventia at the temporal artery biopsy appear to be related to a more benign disease, while large vessel involvement at diagnosis is associated with reduced survival [43].

The role of **genetic and environmental factors** (including infectious etiology) on explanation of geographical differences in GCA epidemiologic studies remains unclear [44]. **Geographical variations, seasonal fluctuation, and cyclic pattern** have been observed in the incidence/prevalence of GCA [44].

A **temporal cyclic pattern** of GCA incidence with recurrent peaks and valleys every 7–10 years was demonstrated until 1999 in Mayo Clinic cohort, no peak between 2000 and 2009 [5, 22]. Once the hypothesis is the **theory of sunlight** as a risk factor of GCA. In 1965, Kinmont and McCullum reported 14 patients with GCA who experienced serious vascular complication after sun exposure [45]; moreover, they noticed that the incidence was higher in the summer period. The effect of sun on temporal arteries was demonstrated on histologic specimens; in fact, solar radiation seemed to destroy the essential supportive elastic framework of arteries and since the temporal arteries are superficial on the forehead they resulted vulnerable to sun damage [46]. In a recent study from Mayo Clinic, the impact of **geomagnetic effects and the solar cycle** on GCA incidence was investigated [5].

They reported that GCA rates peaked 0–1 year after strong magnetic activity, possibly suggesting that the effect is cumulative or that the latency between environmental exposure and disease manifestation could be related to complex autoimmune process [47].

However, in the same study [5], they calculated the correlation between solar extreme ultraviolet radiation and GCA incidence but it didn't reach the statistical significance as the geomagnetic impact [47].

Several studies investigated the **seasonality fluctuations** of GCA incidence [48], but this has been a controversial theory. Few studies reported a significant association between the onset of GCA and a specific season or a certain annual fluctuation [10, 13, 21, 28, 32], but the trend is not consistent, some found a peak in summer some other in winter. A Swedish study described a GCA peak in autumn and winter [13] in the UK and Israel studies in spring and summer [10, 32]. There seems to be no overall consensus on seasonality and incidence rate of this disease. A possible explanation could be that the seasonal variation could be associated with peaks of certain infection.

Autoantibodies against various bacterial and/or viral strains (e.g., parainfluenza viruses, adenovirus, respiratory syncytial virus, measles virus, herpes virus type 1 and 2, Epstein–Barr virus and parvovirus B19) have been investigated as possible triggers in susceptible hosts but with inconclusive results [49, 50]. Some studies using advance DNA sequencing techniques revealed abundant quantity of **bacteria and viral DNA** in the arterial wall of patients with GCA [51]. Genetic material from Chlamydia pneumonia [52], from parvovirus B19 [53] as well as Varicella Zoster antigen [54] was detected in temporal artery specimens. However, these results were not confirmed by other authors [55, 56].

In a US retrospective study, data from Medicare and Truven Analytics MarketScan including 16 million individuals reported that previous herpes zoster infection was associated to an increased risk of 2.2 times higher to develop GCA. If patients had been treated with anti-viral therapy, the risk of GCA decreased even below the background risk of the general population (HR0.67 according to Medicare data) [57].

Socioeconomic level as well as **urban** versus **rural living** have been evaluated as possible predictor of GCA development. In a nationwide Swedish study educational level, family income, marital status, and occupation seemed to have only a weak correlation with GCA occurrence [58]. In a British study, a lower socioeconomic status was associated with ischemic symptoms manifestations resulting from GCA. The possible explanation was that individuals living in more deprived areas do not attend medical out-patient clinic as early and therefore are delayed for diagnosis and treatments [59].

Some studies have found a trend, without reaching the statistical significance, that urban lifestyle may predispose individuals to develop GCA [58]. In Northern and Southern Germany, GCA was significantly more prevalent in urban areas compared to rural areas, and it was not clear if it was related to underdiagnosis of GCA in the rural regions due to differences in the healthcare assistance in cities versus rural area [60].

In a recent letter, Brekke LK et al. reported that in the 41-year incidence study conducted in northwestern Norway a mixed urban and rural area, no difference in GCA incidence was detected in urban compared to rural areas [61].

2.2 Genetics

Female sex is the most important **genetic risk factors** for GCA as reported above.

Several studies have outlined the implications of genetic variants on immune and inflammatory pathways in GCA susceptibility since this vasculitis is a **polygenic disease** [62]. Polymorphisms of the HLA II gene in particular the presence of **HLA DRB1*04 alleles** (both HLA DRB1*0401 and HLA DRB1*0404) are systematically associated with GCA supporting the thesis that GCA is driven by an antigen-based immune response [62]. A recent large-scale genetic analysis on GCA was conducted on 1651 case subjects with GCA and 15,306 unrelated control subjects form six different countries of European ancestry using Immunochip array [63]. The study confirmed the involvement of HLA class II region in the pathophysiology of GCA and the association of GCA with HLA DRB1*04 alleles. Moreover, they identified **HLA-DQA1** as an independent novel susceptibility factor, in particular the presence of the classical alleles DQA1*0101, DQA1*0102, and HLA-DQA1*03:01. The level of statistical significance found in the HLA region underlined the importance of **immune system** in the boost of GCA [63]. In the same study, a test on polymorphic amino acid positions revealed DRB1 13, DQ 47, 56, and 76 are relevant for disease occurrence [63].

Mackie SL et al. demonstrated that the susceptibility of HLA DRB1*04 were better explained by amino acids risk residues V, H, and H at positions 11, 13, and 33 [64] in contrast with previous proposal of amino acids in the second hypervariable region [65]. The authors also performed a meta-analysis on geographic distribution of HLA-DRB1*04 and the frequency of GCA. They reported that GCA incidence was independently associated both with the presence of HLA-DRB1*04 and with latitude itself, concluding that different HLA-DRB1*04 frequency in the population can partially explain variations in GCA incidence.

Association between clinical features of GCA patients and the presence of HLA DRB1*04 were reported, in particular higher visual loss and glucocorticoid resistance were documented among GCA patients and the occurrence of HLA DRB1*04 [66, 67].

Among non-HLA genes, polymorphism of genes that encode for **cytokines** (TNF, IFN-g, IL-10, IL-4, IL-6, IL-18, monocyte chemotactic protein-1, IL-12/IL-21, and IL-12 receptor bet2), for molecules involved in endothelial function and genes of innate immune response have been associated with the appearance or the severity of GCA [68].

A recent GWAS analyzed 1,844,133 **genetic variants**, apart from confirming HLA class II as the most important genetic risk factor for GCA, additional genes were identified: plasminogen (PLG) and prolyl 4-hydroxylase subunit alpha 2 (P4HA2) [69]. PLG encodes a secreted blood zymogen involved in angiogenesis and in a wide spectrum of physiological process including wound healing, fibrinolysis, and lymphocites recruitment. The PLG risk alleles seemed to unbalance the metabolism of its encoded proteins leading to the pro-inflammatory features of GCA [69].

P4HA2 encodes a protein critical for collagen biosynthesis, and it is considered an important hypoxia response gene [69].

Genetic variants of the protein tyrosine phosphatase, non-receptor type 22 (PTPN22) are identified as risk factors for GCA [68]. PTPN22 is involved in the negative control of T cell receptor signaling and in the response of Th17 cells that are considered crucial in the pathogenesis of GCA [70].

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