Seasonal incidence of biopsy-proven giant cell arteritis: a 20-year retrospective study of the University of California Davis Medical System

K.K. Gokoffski[1,2], A. Chatterjee[3], S.K. Khaderi[1,4]

[1]Department of Ophthalmology, Roski Eye Institute, University of Southern California, Los Angeles, CA;
[2]Department of Ophthalmology and Vision Science, University of California Davis, Sacramento, CA;
[3]Department of Statistics and Bio Statistics, California State University East Bay, Hayward, CA;
[4]Department of Ophthalmology, Moran Eye Center, University of Utah, Salt Lake City, UT, USA.

Kimberly K. Gokoffski, MD, PhD
Ayona Chatterjee, PhD
S. Khizer Khaderi, MD, MPH

Please address correspondences to:
Kimberly K. Gokoffski,
Department of Ophthalmology,
Roski Eye Institute,
University of Southern California,
1450 San Pablo Street, 4th Floor,
Los Angeles, CA 90033, USA.
E-mail: kimberly.gokoffski@med.usc.edu

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ABSTRACT

Objective. *Giant cell arteritis (GCA) is a vasculitis that affects large- and medium-sized arteries. The aetiology of GCA is unknown and numerous risk factors have been proposed. In this article, we evaluate the incidence of biopsy-positive GCA in Northern California and assess for seasonal variation.*

Methods. *We performed a retrospective review based on billing codes of temporal artery biopsies performed at the University of California, Davis from 2003 to 2014.*

Results. *We identified 174 biopsies (119 female, 55 male). Of these, 21 positive biopsies were female while 8 were male. Although three times as many women had a positive biopsy compared to men, twice as many biopsies were performed on women. Women were not found to have a significantly higher risk of developing GCA over men. Patients with a positive biopsy averaged 76.4±8.9 years of age. The odds of having a positive biopsy increased significantly with age. Positive biopsies were significantly more likely to occur in the months of May through July than the rest of the year ($p<0.028$).*

Conclusion. *Our retrospective study is the first report of the seasonal incidence of biopsy-proven GCA in California. Our data suggest that increased age and summer months are risk factors for developing biopsy-proven GCA in our region.*

Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, is a vasculitis that affects medium- and large-sized arteries [reviewed in (1)]. Patients can present with a variable constellation of ischaemic symptoms including headache, scalp tenderness, jaw claudication, stroke, transient visual obscurations, diplopia, and vision loss. Because the time interval between severe monocular to binocular involvement is unpredictable, ranging from minutes to years, rapid diagnosis and implementation of treatment is essential.

The gold standard for diagnosing GCA is via a temporal artery biopsy (TAB), which will show various levels of inflammation from pockets of non-granulomatous inflammation of the vessel wall with patchy loss of the internal elastic lamina to frank infiltration with multi-nucleated giant cells (Fig. 1) (2). The sensitivity of a TAB is limited by the patchy nature of the disease and the fact that often time, patients have already been started on steroid treatment before a biopsy can be performed. Ultrasound of the temporal artery has been found to have a higher sensitivity than the TAB but also a lower specificity (3). Thus, the American Board of Rheumatology has put forth clinical criteria for diagnosing GCA (4). Three of the following five criteria are required for a clinical diagnosis of GCA:

a. Age of onset >50 years
b. New onset headache
c. Temporal artery abnormality (tenderness or decreased pulse on palpation)
d. Increased ESR (>50mm/hr by Westerngreen)
e. Abnormal temporal artery biopsy

The aetiology of GCA is unknown: age, female gender, and Scandinavian ancestry have been touted as risk factors. Studies have shown that GCA almost exclusively affects patients over the age of 50, with increasing incidence with increasing age (5). Females are affected more often than males, on average at about a 2:1 ratio (6, 7). Geo-epidemiologic studies suggest a higher incidence in Caucasians, specifically Scandinavians, over southern Europeans, Asians, Middle Easterners, Africans and Australians (8).

In addition to these non-modifiable risk factors, many groups have reported seasonal variation in the incidence of GCA, with some observing a higher incidence in the summer months (9), while others found the incidence to be higher in the winter months (10, 11). One proposed explanation for the seasonal variation in GCA incidence is seasonal exposure to infectious antigens such as Mycoplasma, Parvovirus, and Chlamydia (12) or reactivation of varicella zoster virus (13). To assess whether there is seasonal variation in GCA incidence in Northern California, we performed a retrospective review of temporal artery biopsies performed at the University of California, Davis.

Methods

Medical records of every patient who underwent a temporal artery biopsy (TAB; CPT code 37609) at the University of California, Davis Medical Center (UCDMC) or was given the diagnosis of giant cell arteritis (ICD9 code 446.5) between 2003 and 2014 was reviewed. The year 2003 was selected for ease of accessibility, as this was the year the electronic medical record system was instituted at UCDMC. We recorded patient demographics, onset and nature of presenting symptoms as reported by the patient, date of biopsy and, when possible, visual acuity and lab values. The institutional review board of the University of California, Davis Medical Center, approved this study. Patients were excluded if they were given a diagnosis of GCA from a TAB from an outside hospital.

Census data

The University of California, Davis Medical Center is a tertiary referral center that primarily treats patients from Sacramento County but whose catch pool extends to the Oregon border and includes Nevada. To perform incidence calculations, the total number of female and male patients who achieved a maximum age of 50 years or greater between the years 2003 and 2014 in the University of California Davis Medical System electronic medical records was obtained from Cohort Discovery, a repository of de-identified patient data.

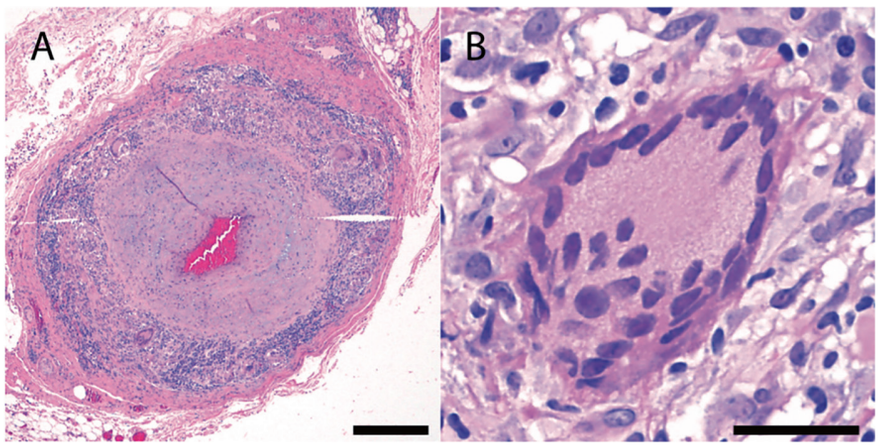

Fig. 1. Temporal artery biopsy showing lymphocyte and giant cell infiltration.
A: Histologic cross-section of temporal artery biopsy stained with Haematoxylin and Eosin. Scale bar, 200μm. **B**: Magnified view of giant cell found in vessel wall. Scale bar, 20μm.

Statistics

Chi square analysis was performed to determine if the outcome of the biopsy results were independent of gender. Similar Chi-square tests were performed to check for association between age group and biopsy outcome as well as summer months and biopsy outcomes. To understand the nature of the relationship between age group and season of onset with the biopsy results, we further investigated with an appropriate regression model. Given the binary nature of the data (positive or negative biopsy outcome), we performed Logistic regression analysis on our data set with the biopsy outcome as our response variable and gender, age group and season (summer-non summer) as the three categorical predictors. We also looked at the odds ratio from our Logistic regression analysis to understand the effect of gender, age and season on the risk of having a positive biopsy.

Results

Case identification

A query of the UCDMC electronic medical records for patients who underwent temporal artery biopsy (TAB) or were given a diagnosis of GCA between 2003 and 2014 rendered 517 charts. Three hundred forty-two charts were excluded because they were duplicate inquiries, erroneous charting, or because no biopsy was performed. One chart was excluded because the biopsy was performed in 1995.

Of the 174 charts included in the study, 119 TABs were performed on females while 55 were performed on males. There were 29 positive biopsies: 21 female and 8 male. The mean age of patients with a positive biopsy was 76.4 ± 8.9 years. Although three times as many patients with a positive biopsy were female, twice as many women were biopsied as men (Table I). By chi square analysis, women were not found to have a significantly higher risk of developing GCA over men ($p<0.61$) in the Sacramento Community. Although odds ratio estimates suggest that the odds of having a positive biopsy decreases by 1.14 times when the gender changes from female to male, gender does not appear to be a significant predictor for biopsy results (Table II).

Incidence of biopsy-proven GCA

As there are many distinct multi-provider groups in the Greater Sacramento County, we were concerned that obtaining general Sacramento demographics from the US Census Bureau to calculate incidence would lead to underestimation. Instead, we used the total number of patients enrolled at UCDMC during our study period to calculate GCA incidence.

Demographic information describing the UCDMC community was obtained from Cohort Discovery from 2003 to 2014. The overall incidence of biopsy-proven GCA was 7.9 per 100,000 over 50 years of age. The incidence of GCA was 10.7 per 100,000 for females and

Table I. Female gender does not portend an increased risk for GCA in the UCDMC community (p<0.61).

	Positive biopsy	Negative biopsy	Total
Female	21	98	119
Male	8	47	55
Total	29	145	174

Table II. Regression coefficients and odds-ratio estimates obtained from logistic regression in SAS.

Analysis of maximum likelihood estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1.1032	0.5451	4.0957	0.0430
Gender	F	1	-0.1300	0.4754	0.0748	0.7844
Season	1	1	-0.7824	0.4522	2.9939	0.0836
Age	50-59	1	2.6822	1.0794	6.1751	0.0130
Age	60-69	1	1.1630	0.5427	4.5928	0.0321
Age	70-79	1	0.6278	0.5215	1.4489	0.2287

Odds ratio estimates			
Effect	Point estimate	95% Wald confidence limits	
Gender: female vs. male	0.878	0.346	2.230
Season: summer vs. non-summer	0.457	0.189	1.109
Age: 50-59 vs. >80 yrs	14.618	1.762	121.238
Age: 60-69 vs. >80 yrs	3.199	1.104	9.268
Age: 70-79 vs. >80 yrs	1.873	0.674	5.207

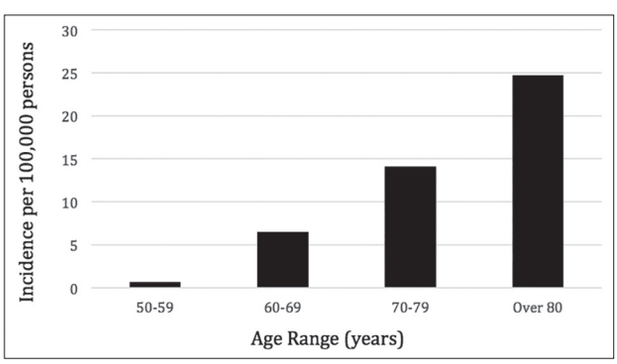

Fig. 2. The incidence of GCA increases with increasing age (p<0.01).
Incidence of biopsy-positive GCA per 100,000 in Northern California plotted by age group.

Table III. Chi square analysis suggests a statistically significant increase in GCA incidence in the summer months at UCDMC (p <0.028).

	Positive biopsy	Negative biopsy	Total
Summer months	**12**	32	44
Non-summer months	17	113	130
Total	29	145	

4.6 per 100,000 for males over 50 years of age.

Similar to other groups (6, 9), we found the incidence of biopsy-proven GCA to increase with increasing age. Between ages 50 to 59, the incidence was 0.68 per 100,000 and increased to 6.5 per 100,000 for ages 60 to 69, 14.1 per 100,000 for ages 70 to 79, and 24.7 per 100,000 for those over 80 years of age (Fig. 2). A chi-square test of association between outcome of biopsy and the four age groups resulted in a p-value of 0.01 implying a significant association between age and biopsy outcome. From Table II, we can further conclude that there are significant differences in biopsy results between age groups 50 to 59 and > 80 years and 60 to 69 and > 80 years. By observing the odds ratio estimates for each age group, we found the odds of having a positive biopsy increases significantly with age (Table II). An individual whose age is over 80 years is almost 15 times more likely to have a positive biopsy as compared to someone aged 50 to 59 years.

Seasonal incidence of GCA

To assess seasonal incidence of biopsy-proven GCA, we chose the date of the biopsy, as opposed to date of onset of GCA symptoms, as the time of onset because that latter is unreliable, highly variable and not always attainable. At UCDMC, 44 biopsies were performed during the months of May, June, and July while 130 were performed during the other months (Table III). Of the 44 summer biopsies, 12 were positive while 32 were negative. Of the 130 non-summer biopsies, 17 were positive while 113 were negative. Chi square analysis demonstrated a statistically significant increase in GCA incidence in the warmer months of May, June and July at UCDMC (p<0.028).

When logistic regression analysis was performed, season (summer versus non-summer months) was found to be a significant predictor of biopsy outcome at a 10% significance level. In Northern California, the odds of having a positive biopsy is 2.2 times higher in the summer months as compared with the non-summer months (Table III).

Discussion

Regional variation in incidence of GCA around the world

To better understand how the incidence of biopsy-proven GCA at UCDMC compares to other parts of the world, we performed a review of the literature. Table IV summarises the results of our literature search. If biopsy-proven rates were not available, clinical incidence was reported and noted.

It was not surprising to find that almost all studies reported an increased incidence of GCA with increasing age (6, 9). For example, Mohammad *et al*. found the risk of biopsy-proven GCA to be 2.0 per 100,000 during the 5th decade of life, significantly lower than

Table IV. Summary of the reported incidence of GCA in the world.

Article	Location	Interval	#of pts included	#of positive biopsies (%)	Mean age	F:M Or % Female	Incidence/ 100,000 over 50 years of age	Peak incidence
North America								
Ramstead *et al*. (32)	Saskatoon, Saskatchewan	1998 – 2003	141	37 (26%)	76.5±8.2	2.4:1	9.4	Not evaluated
Mader *et al*. (27)	Alaska	1983 – 2003	122 with clinical diagnosis	3 of 20 biopsies performed	72	2:1	1	Not evaluated
Pereira *et al*. (8)	San Francisco, CA	1990 – 2006	38	38	77±7	73.6%	Not assessed	20-fold decreased incidence in Asians relative to Caucasians.
Gokoffski *et al*. Current work	Sacramento, CA	2009-2014	174	29	76.4	72.4%	7.9	Increased incidence in May-July
Liu *et al*. (22)	Los Angeles, CA	1986 – 1998	121	20 (16.5%)	75.2 ± 5		Not assessed	GCA affects Whites, not Asians, Blacks or Hispanics.
Huston *et al*. (33)	Olmstead, Minnesota	1950 – 1974	42	38	75		11.7	
Machado *et al*. (7)	Olmstead, Minnesota	1950 – 1985	94	88			16.8 biopsy and clinical diagnosis	
Salvarani *et al*. (34)	Olmstead, Minnesota	1950 – 1999	173	151 (87.3%)	74.8	79.2%	18.8 (95% CI 15.9 to 21.6)	Cyclic peak occurring every 7 years and lasting 3 years but not statistically significant
Kisza *et al*. (35)	Philadelphia, PA	1994 – 2011	744	215	77.3	74%	Not assessed	No statistically significant change in incidence by season
Smith *et al*. (20)	Shelby, Tennessee	1971 – 1980	93	21	72	23:3	1.58 biopsy proven and probable	Incidence in Whites was 7 fold higher than Blacks.
Lam *et al*. (23)	Miami, FL	1996 – 2002	257	44			Not assessed	Rates of biopsy-proven GCA were similar between Hispanic and Non-Hispanic patients.
South America								
Souza *et al*. (18)	Sao Paulo and Rio de Janeiro, Brazil	2009 – 2010	45	16	73	1.8:1	Not assessed	
Europe								
Gran *et al*. (36)	South Norway	1987 – 1994	322	66			29	
Haugeberg *et al*. (37)	Vest Agder County, Norway	1992 – 1996	53	94%	72.7	2:1	29.1	Not assessed
Bengtsson *et al*. (38)	Goteborg, Sweden	1973 – 1975	126	74			16.8	Not assessed
Petursdottir *et al*. (11)	Goteborg, Sweden	1976 – 1995	4971	665 (13.4%)			22.2	No cyclical fluctuation but statistically significant peaks in late winter autumn months
Nordborg *et al*. (39)	Goteborg, Sweden	1977 – 1986	2307	284 (12.5%)			18.3	
Noltorp *et al*. (21)	Southern Sweden	1986 – 1987	29	8	72		33.6	Not assessed
Mohammad *et al*. (6)	Skane, Sweden	1997 – 2010	4216	840	75.9	74.5% 3:1	14.1	No seasonal variation
Franzen *et al*. (40)	Western Nyland, Finland	1984 – 1988	54	16	74	2.25:1	17.4 retrospective 26.2 prospective	Not tested
Baldursson *et al*. (41)	Iceland	1984 – 1990	744	125 (16.8%)	71.9		25.4 biopsy proven	Not tested
Elling *et al*. (12)	Denmark	1982 – 1994	2651	15%	64.5		15.1 biopsy proven	Distinct peaks that correlated with epidemics in Mycoplasma, Chlamydia pneumonia, parvovirus B19.
Jonasson *et al*. (10)	Lothian Region, Scotland	1964 – 1977	136	136	73	2.87	4.32	Peak occurrence in January.

Article	Location	Interval	#of pts included	#of positive biopsies (%)	Mean age	F:M Or % Female	Incidence/ 100,000 over 50 years of age	Peak incidence
Smeeth *et al*. (9)	United Kingdom	1990 – 2001	3928 with clinical diagnosis	Biospies were not reviewed	72.8	2.6:1	2.2	More likely to be diagnosed during summer months.
Duhaut *et al*. (30)	Rhone-Alpes, France	1991 – 1997	292	207	74.1 male 75.6 female		Not assessed	Increased incidence of positive biopsy during autumn or winter months
Barrier *et al*. (42)	Loire, France	1970 – 1979	110	100		1.97	9.4 (55yrs and older)	No seasonal pattern noted.
Reinhold-Keller *et al*. (28)	Germany	1994	79 with clinical diagnosis	Biospies were not reviewed	76	4.7:1	24 Northern vs 30 Southern Germany	2.25 fold increased relative risk for older urban patients over older rural patients.
Gonzalez-Gay *et al*. (25)	Lugo, Spain	1981 – 1998	161	161			10.24	No seasonal pattern noted.
Salvarani *et al*. (43)	Reggio Emilia, Italy	1980 – 1988	43 with clinical diagnosis	20	67.6±10		6.9	Not evaluated
Catanoso *et al*. (26)	Reggio Emilia, Italy	1986 – 2012	836	285	74.4±7.3	7.8:3.3 incidence	5.8	No seasonal variation: 22.5% in winter, 26.7% in spring, 26.7% in summer, 24.2% in autumn
Middle East								
Bosley T *et al*. (44)	Saudi Arabia	1982 – 1998	72	4			Not assessed	Too few to calculate
Chaudhry *et al*. (45)	Riyadh, Saudi Arabia	1983 – 2004	102	7 (6.8%)	71.7±8.6		Not assessed	
Jokar *et al*. (46)	Mashad, Iran	2002 – 2012	30 with clinical diagnosis	15	63.9±10.4	1:1.1	Not assessed	
Pamuk (47)	Northwestern Turkey	2002 – 2008	72	19	70±6.8		1.13	
Friedman *et al*. (48)	Israel	1960 – 1978	46	46		0.95	0.49	
Sonnenblick *et al*. (49)	Jerusalem, Israel	1980 – 1991	109	84	74.2	65%	10.2	Increased incidence during May and June.
Bas-Lando *et al*. (50)	Jerusalem, Israel	1980 – 2004	206	170		1.4:1 F: M ratio	9.5 biopsy proven	Cyclical pattern occurring 8-10 years apart. Although not statistically significant, peak incidence May and June.
Asia								
Singh *et al*. (51)	Mumbai, India	1990 – 2005	21	10	66.5	1:1	Not assessed	
Mathew *et al*. (52)	India	2005 – 2010	15 with clinical diagnosis	11	67.53±9.13	1:1.5	Not assessed	
Sharma *et al*. (53)	India	2008 – 2014	72	5	67		Not assessed	
Kobayashi *et al*. (54)	Japan	1997	66	30	72.5±10.3	1.7:1	1.47 (prevalence)	
Imai (55)	Shizuoka, Japan	2001 – 2008	19 with clinical diagnosis	11	78.1±4.8	1.1:1	Not assessed	
Attaseth *et al*. (19)	Bangkok, Thailand	2005 – 2014	236	6	72.5	33%	Not assessed	
Africa								
Khalifa *et al*. (56)	Tunsia	1986 – 2003	96	96 Biopsy proven and clinical diagnosis	70.8±7.7	1:0.88	7 (prevalence)	
Australia								
Abdul-Rachman *et al*. (57)	Otago Region, New Zealand	1996 – 2005	363	70 (19%)	72.8±8	2.8:1	12.7	Cyclical pattern occurring every 5 years. No statistically significant seasonal variation.
Dunstan E *et al*. (58)	Southern Australia	1992 – 2011	314	314	78	72%	3.2	Increased incidence in summer months (December to January).

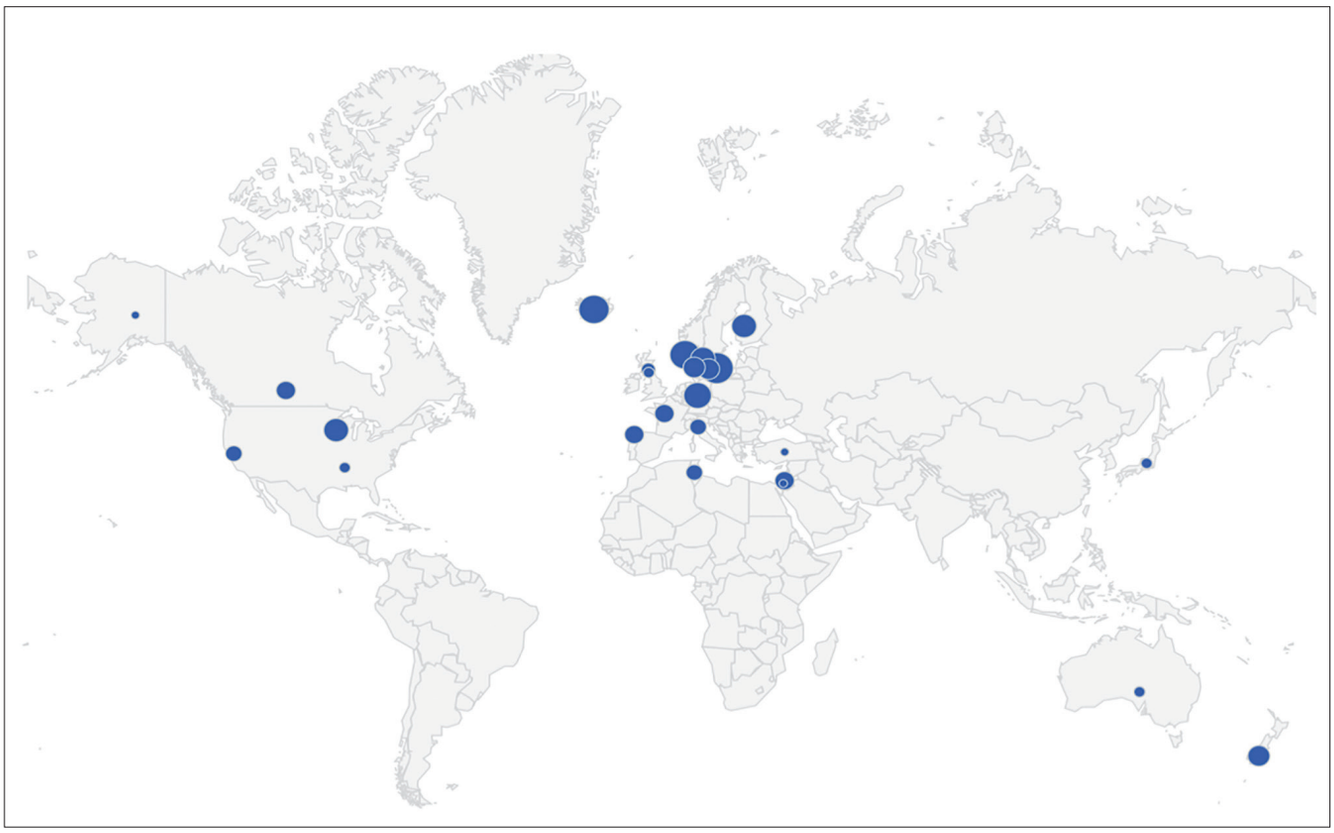

Fig. 3. Reported incidence of GCA around the world by region.
The relative incidence of GCA around the world (summarised in Table III) is represented by the area of the dot.

the incidence of 31.3 per 100,000 in the 7th decade of life. As mentioned above, we found a similar result in the UCDMC population: increased incidence of GCA was associated with increased age. GCA incidence was 0.68 per 100,000 for patients in their 5th decade of life, significantly lower than the incidence of 24.7 per 100,000 in patients over 80 years of age ($p<0.0001$).

Most studies also reported an increased incidence of GCA in women (6) and not men (7). Although in our study, three times as many of the patients with biopsy-proven GCA at UCDMC were women, twice as many women were biopsied compared to men. Thus, women were not found to be at higher risk for developing GCA at UCDMC compared to men.

The geographic distribution of reported GCA incidence around the world is depicted in Fig. 3. As can be seen from Fig. 3 there is a paucity of data from large spans of the world, including Central and South America, Africa and Asia. Although multiple case reports can be found in the literature, few reports of incidence can be found from these regions (14-19). Of the reports that were available, the reported incidence of GCA is higher in Caucasians (20), particularly Scandinavians, than other ethnicities. The highest rate was found in Southern Sweden, around 33.6 per 100,000 (21). The lowest reported rates were of Alaskan Natives, Blacks, Asians, and Hispanics. A small retrospective series from UCSF found a 20-fold decrease in the incidence of GCA in self-reported Asians over Caucasians, with an estimated incidence between 0.09 and 1.5 per 100,000 in Asian-Americans (8). In a retrospective review of patients in Los Angeles County, Liu *et al*. found no cases of biopsy-proven GCA in either Hispanic or African American populations (22). This contrasts with results from Bascom Palmer where authors detected similar rates of GCA in self-identified Hispanics as Non-Hispanics (23). The difference could be attributed to the primarily Mexican-Hispanic population assessed by Liu *et al*. versus the primarily Cuban-Hispanic population assessed by Lam *et al*. In Shelby County, the incidence of GCA was 7-fold higher in Whites than Blacks (20). Interestingly, the Black patients with biopsy-proven GCA were younger (age 47 and 53) than affected Whites.

The incidence at UCDMC was found to be 7.9 per 100,000 registered patients over 50 years of age, about average when compared to the other reported incidence rates around the world. Given the diverse demographics of Sacramento, California, which was claimed by TIME magazine in 2002 to be the most diverse city in the United States (24), this was not an unexpected finding.

The incidence of GCA in Scandinavian countries is markedly higher than southern European countries including Spain and Italy [see Table IV, (25, 26)]. Given the influence of season on GCA incidence, this lead us to wonder whether higher latitude might account for this difference and represent another unidentified risk factor for GCA. Lack of consistency in methods of measuring incidence rates globally along with insufficient access to complete data

sets precludes us from formally testing this hypothesis statistically. Arguments against this hypothesis include the low incidence of GCA in Alaskan Natives (27), who live at a similar latitude as many Scandianvians. Further opposing evidence, Smeeth *et al*. found a higher incidence of GCA in southern over northern UK (9). Interestingly, a study comparing GCA incidence in rural versus urban Germany found a 2.25-fold higher relative-risk for older urban patients than older rural patients (28). Although under diagnosis in rural areas could account for this difference, the authors propose increased exposure to pollutants as an explanation for the increased incidence in their cities. Others have postulated a theory of genetic predisposition leading to increased T cell activation [*e.g*. HLA-DR4; (29)] to explain the higher incidence in Sweden and Minnesota (which also has a high Scandinavian population).

At UCDMC, we found a statistically significant increase in the incidence of GCA during the months of May to July compared to the rest of the year. Of the groups that evaluated for seasonal effect on GCA incidence, there is significant variation around the world. Smeeth *et al*. found a similar increase in GCA incidence in the summer months in the UK (9). Yet, not too far away in Scotland, Jonasson *et al*. found a peak incidence in January (10). In Goteborg, Sweden, Petursdurttir *et al*. found statistically significant peaks in late Winter and Autumn months (11). Catanoso *et al*. found no significant variation in GCA incidence by season (26).

What is responsible for the seasonal variation in GCA incidence? Although the answer to this is difficult to prove, Elling *et al*. put forth the provocative hypothesis of a predisposing infectious antigen (12). In a large retrospective study in Denmark, Elling *et al*. found a close association between peaks of GCA incidence and Mycoplasma, parvovirus, and Chlamydia epidemics (12). A different prospective case control study found a significantly higher association between GCA and anti-parvovirus IgM over controls (30). Moreover, a large retrospective study from the Mayo Clinic spanning almost 50 years found a cyclical incidence to GCA with a peak occurring every 7 years and lasting about 3 years (8), also citing a possible link to parvovirus B19 (31). Varicella zoster virus (VZV) has also been suggested to play a role in inciting GCA given that VZV can cause an occlusive vasculitis that resembles GCA and a recent study found 70% of biopsy-positive GCA patients had VZV antigen in their TAB (13).

Another possible explanation for the discrepancy in season incidence is the different diagnostic criteria used in each study. For example, a study comparing biopsy-positive to biopsy-negative GCA found a higher incidence of biopsy-negative GCA during summer months while biopsy-positive GCA had a higher incidence during winter months (30). In the same study, biopsy-positive GCA was more likely to be associated with higher level of inflammatory markers and severe vision loss while biopsy-negative GCA was more likely to be associated with stroke (30).

Our retrospective study is the first report of the seasonal incidence of biopsy-proven GCA in California. Our data suggests that increased age and summer months are risk factors for developing biopsy-proven GCA. This work suggests that season may be an unrecognised risk factor for GCA that the clinician should consider when screening patients.

Study limitations

There are numerous limitations to this study. This was a retrospective study and thus we were not able to set criteria under which TABs would be performed. Moreover, we did not directly review the pathology specimens of each biopsy. Also, although UCDMC is a tertiary care centre, it is not the only care provider for the Greater Sacramento Area. There are likely to be a number of patients with GCA that are being diagnosed and treated by other facilities in the area including Kaiser Permanente, Sutter Health, and Mercy Medical Group. Although we assume that UCDMC treats an equal proportion of GCA patients as the other facilities, differences in patient demographics may invalidate this assumption. Additionally, because we excluded patients that were treated empirically, our calculations could have under-estimated the incidence of GCA.

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