FULL TITLE: Projected worldwide disease burden from Giant Cell Arteritis by 2050.

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ABSTRACT

OBJECTIVE: To estimate and project the number of people affected worldwide by Giant Cell Arteritis (GCA) by 2050. Modeling the number of people visually impaired as a result of this disease will help establish the projected morbidity and resource burden.

METHODS: A systematic literature review up to December 2013 was conducted using PubMed and ISI Web of Science. Studies reporting an incidence rate for GCA were used to model disease incident cases at regional and national levels. UN Population Prospect data were used for population projections. Morbidity burden was established through rates of visual impairment. The associated financial implications were calculated for the United States of America.

RESULTS: The number of incident cases of GCA will increase secondary to an ageing population. By 2050, more than 3 million people will have been diagnosed with GCA, in Europe, North America and Oceania. Approximately 500,000 people will be visually impaired. By 2050, in the USA alone, the estimated cost from visual impairment due to GCA will exceed US\$76 billion. Inpatient care for patients with active GCA will total approximately US\$1 billion. Management of steroid-related adverse events will increase costs further; with steroid-induced fractures estimated to total US\$6 billion by 2050.

CONCLUSION: Projecting disease burden for GCA on a global scale allows for optimization of health care planning and prioritization of research domains. Additional population-based studies are required to more accurately project worldwide disease burden. This work highlights the future global disease burden of GCA, and illustrates the associated financial implications.

KEY WORDS:

Giant cell arteritis, incidence, prevalence, disease burden, blindness, costs

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SHORT TITLE/FOOTLINE: GCA global disease burden

INTRODUCTION

GCA is the most common chronic systemic inflammatory vasculitis affecting people aged over 50 years (1). It has a predilection for medium and large-sized vessels of the head and neck. Obliteration of the arterial lumen leads to its ischaemic complications such as scalp necrosis, jaw claudication, and optic neuropathy. GCA is associated with significant morbidity, mostly through its detrimental effect on vision. Visual manifestations affect approximately 30% of patients, though prompt treatment can prevent permanent, irreversible visual loss (1).

The pathoaetiology of this disease is not currently fully understood, though is likely the culmination of both genetic and environmental stressors. There is no pathognomonic laboratory test or marker to identify this disease (2). The current gold standard to confirm the diagnosis is temporal artery biopsy (TAB). However, the diagnosis can be made clinically despite a negative biopsy result (3), and although merely a classification criteria for GCA, the 1990 American College of Rheumatology (ACR) criteria are widely used by physicians to help make the diagnosis of GCA (3), as well as are frequently used as inclusion criteria in GCA studies.

Despite the availability of new disease modifying drugs, the mainstay of treatment of GCA involves corticosteroids, which are not without side effects. More than half of all patients with GCA experience at least one adverse effect commonly associated with corticosteroid treatment (4), thereby adding further to the morbidity experienced from this disease.

There are high costs associated with managing GCA not only because of the social costs attached to visual impairment. Being a relapsing and remitting disease, GCA requires frequent follow-up for disease activity monitoring and in severe cases may require hospitalization. The added costs associated with managing the side effect and complications of

immunosuppressive treatment must also be considered when determining the disease cost burden.

This aim of this review is to investigate and model the increase in disease burden of GCA over the next 35 years. United Nations (UN) data suggest that in 2050 more than a third of people living in the developed world will be over the age of 60 years (5). As such, the global burden of diseases associated with ageing, such as GCA, is also set to dramatically increase.

METHODS

A systematic review of all publications up to December 2013 was performed using the PubMed and ISI Web of Science databases. The search criteria included: “giant cell arteritis OR temporal arteritis OR Horton's disease” AND “prevalence OR incidence”. Articles written in English, French or Dutch, were reviewed for relevance. PRISMA guidelines were followed (6).

Included studies fulfilled the following criteria: 1) incidence rates were calculated for the studied reference population; 2) a diagnosis of GCA was defined as either having positive temporal artery biopsy, a clearly established clinical definition or meeting the American College of Rheumatology (ACR) classification clinical criteria for GCA; and 3) dates of the study period were clearly stated. Articles were excluded if they did not distinguish between GCA and polymyalgia rheumatic (PMR). When studies were updates of previous cohorts, the most recent study was used and the most current data were incorporated for calculations.

The UN Department of Economic and Social Affairs World Population Prospect data were used for reference population projections (7). Annual estimated population size for people over the age of 50 years between 2014 and 2050 was extracted for each country. Incident data from available studies were used to model national trends. Provided similar demography, incident rates provided for provincial regions were extrapolated to represent

their reference country and were assumed not to change over time. In world regions, as defined by the UN, where multiple country data were available, median (as well as upper and lower limit) incident case estimates were calculated based on the corresponding incidence data of regional countries. Given the differences in methodology and recruitment design between studies, a weighted meta-analysis was not performed. When only two studies were available within a region or continent, the mean rate was used. Incident cases were calculated on an annual basis and then added to provide the total number of cases predicted to be diagnosed with GCA by 2050.

To calculate the projected number of people with visual impairment secondary to GCA, a conservative event rate of 15% was used (1). This is an acceptable average of the potential permanent visual impairment quoted in different papers. Visual manifestations usually are among the presenting symptoms or develop shortly after the diagnosis in approximately 30% of patients and range from transient visual symptoms to permanent visual loss, the latter affecting near to 15% of patients (1). This work attempts to model the costs associated with permanent visual impairment from GCA hence the reason for using this figure.

To determine the likely financial impact of visual impairment from GCA, data from the United States of America (USA) were used as an example. In 2007, the total annual costs associated with visual impairment in the USA was calculated to be US\$53,896 per person (8). Between 1980 and 2004 the mean age at diagnosis of GCA for people in the USA was found to be approximately 75 years of age (9), and mean life expectancy is predicted to be approximately 83.8 years by 2050 (10). As such, by the year 2050 a patient with GCA and visual impairment is expected to live for approximately 9 to 10 years following diagnosis. Generally, GCA is not thought to alter life expectancy and as such this was not incorporated into our model (11). Hence our method for estimating visual impairment-related costs from GCA in the USA over the next decades, consisted of using 15% of the total calculated number of GCA affected

individuals in the USA by 2050, multiplying this figure by \$53,896 to determine the cost burden for one year and then multiplying this further by 10, the average remaining lifespan of a GCA affected individual.

To further highlight the potential financial impact of this disease, an example of a direct cost associated with GCA treatment in the USA was calculated. The quoted cost for managing 44,100 inpatients with GCA in the USA between 1986 and 1990 was estimated to total just over US\$355 million (12). Thus, US\$8049 per patient for each admission to hospital was used for projecting the costs of inpatient care. Projected numbers of inpatient admissions were based on the assumption that those with visual loss, i.e. 15% of the total GCA affected population in the USA, are likely to require at least one episode of inpatient hospital care when diagnosed. Given that GCA generally manifests and is diagnosed well after the age at retirement no indirect costs (loss of productivity) were considered.

The costs for managing corticosteroid-related complications, an important additional financial burden from GCA, was also calculated. Steroid use in GCA is usually of prolonged nature. A North American suggested that the median time for glucocorticosteroids to be discontinued and permanent remission to occur is 21.6 months (4). In this paper those patients experiencing an adverse event, the median time from initiation of therapy to the first adverse event was 1.1 years. As most patients with GCA will be on corticosteroid treatment for an average of 1-2 years, there is unfortunately sufficient time for them to experience a complication from the treatment. Being one of the most common adverse events, occurring in up to 38% of patients with GCA, the incidence of corticosteroid-induced fractures was modeled (4). The cost of managing a corticosteroid-induced fracture for one patient was estimated to total US\$18,358 (13). Effect of inflation and discounting on healthcare costs were not included in our model and as such all figures should be considered in present day values (14, 15)

RESULTS

The search yielded a total of 702 articles in PubMed and 430 in ISI Web of Science. All relevant publication identified through ISI Web of Science search, had been identified through PubMed. After abstract and full-text review 14 (2.0%) met the inclusion criteria (Table 1). All of the included studies were retrospective and detailed their calculated incidence rate for the region within the country of origin. All studies used either primary care databases or hospital medical records to identify the number of people diagnosed with GCA over a particular period, and/or searched histopathology databases to record the number of positive temporal artery biopsies (Table 1).

Data from included studies were used to model the **burden of incident cases of GCA** (Supplementary Table 1), and summary results for corresponding world-regions are displayed in Table 2. There were sufficient country data to calculate the projected number of GCA cases likely to be diagnosed by 2050 within Europe (including Denmark, France, Iceland, Italy, Norway, Spain, Sweden and the United Kingdom), North America (Canada and The United States of America) and the Oceania region (Australia and New Zealand). At least 3 million people are expected to be diagnosed with GCA by 2050 in these world regions alone. Approximately half a million people are predicted to become blind from GCA over the next 35 years (Table 2). The number of incident cases of GCA in these three regions is predicted to increase secondary to the increase in population aged over 50 years (Supplementary Table 2). However, in Europe the peak of incident cases is predicted to occur in 2040, after which the overall population is expected to decline.

If current treatment regimens remain unchanged, over 140,000 patients diagnosed with GCA in the USA will present with acute visual symptoms and receive hospital admission for treatment such as administration of intravenous corticosteroid (Supplementary Table 3). By 2050, US\$1.13 billion is expected to have been spent on inpatient GCA management in the

USA. Between 2014 and 2050, the estimated cumulative cost from visual impairment for patients diagnosed with GCA will be US\$70.63 billion in the USA alone.

There are significant treatment related side effects **resulting from the use of corticosteroid medication in patients with GCA.** Up to 80% of GCA patients requiring long-term corticosteroids to achieve disease remission will develop a steroid related adverse event (4). By 2050, just under 360,000 patients in the USA with GCA are expected to have developed a steroid-induced fracture, at a total estimated cost of management mounting to over US\$6.58 billion (Supplementary Table 3).

DISCUSSION

There have been no previous estimates of the global impact of GCA. This work highlights the significant morbidity, including visual impairment, and financial impact that GCA is likely to cause in the future. Using currently available incidence data, we have provided a detailed estimate on the projected impact of GCA. It was possible to calculate the projected number of people who are likely to be diagnosed with GCA across North America, Europe, and Oceania. GCA is primarily a disease of Caucasians of European origin and hence, by addressing these world regions, the findings reflect the areas most affected by the disease.

Our work highlights the increasing socioeconomic burden from GCA over the next 35 years, assuming there are no major breakthroughs in disease screening, prevention or treatment. By 2050, an average of 3 million people will have been diagnosed with GCA (Table 2). In the Oceania region, the number of GCA incident cases is predicted to double over the next 35 years.

Approximately 500,000 people will become blind from GCA by 2050. Given the variation in reported rates of visual impairment, this figure is likely to underestimate the actual number.

Prompt treatment significantly reduces the risk for visual loss in the disease and advances in diagnosis as well as treatment will hopefully mitigate some of these adverse sequelae.

There are considerable socioeconomic consequences for sudden visual loss secondary to GCA (16). Many elderly patients who are visually impaired require extensive social support. Across France, Germany, the United Kingdom and Italy the rates of institutionalisation for visually impaired persons is reported to range from 7.8% to 10.9% (17). Visual impairment and blindness have important implications for resource allocations, causing marked economic burden (18). Although cost implications are clearly country dependent, we found the total projected costs related to visual impairment from GCA in the USA alone is US\$76 billion. The financial implications globally will certainly be much greater.

Additionally, should prolonged steroid treatment remain the primary treatment modality in GCA, there will be additional costs from managing side effects and associated complications. We calculate that, in the USA alone over 800,000 people with GCA will be expected to develop complications from treatment. Whilst the cost of corticosteroids is low, their total costs may be considerably higher when the costs of managing short and long term adverse events are considered (13). In a recent Australian study, approximately 90% of GCA patients reported side effects from corticosteroids (19). This is supported by a Brazilian study which showed a similar proportion (91.1%) of GCA patients developed a steroid related complication (20). In the USA, at least one side effect from corticosteroids was identified in 86% of GCA patients; whilst two or more side effects were reported in just under 60% of patients (4). We calculated that by 2050, over 350,000 patients will have sustained a steroid-induced fracture in the USA alone. This will cost the US healthcare system an estimated US\$6 billion. Again, although costs inevitably vary between countries, this figure puts into perspective the implications of current GCA treatment and potential future impact globally.

This study has highlighted the paucity of available epidemiological data on GCA. It was not possible to predict the global disease burden of GCA. Whilst GCA has been most extensively described in European-derived Caucasian populations, it is also recognized amongst people of different ethnic groups (such as the Indian, Chinese, Africans and Latin Americans). In omitting these world regions from our future predicted GCA calculations, especially China and India which together comprise close to one third of the world's population, we are substantially under-representing the overall impact of this disease worldwide. Prevalence studies in these regions are clearly required to more accurately project the potential global disease burden of GCA.

Case reports and a number of case series have highlighted the fact that GCA can affect people of any racial background. African-American people accounted for 13% of patients with a diagnostic temporal artery biopsy from a hospital-based study in Washington (21). Similarly, there have been a number of reported cases of GCA amongst people of Chinese ethnicity (22-24). Interestingly an increase in prevalence of GCA has been found between two Japanese-based performed in 1997 (25) and 2001-2008 (26). Nonetheless, it has been estimated that the rate of GCA in people of Asian ethnicity is approximately 20 times less common than their Caucasian counterparts (27, 28). There are also reports of GCA in people of Indian descent (29) (30).

In Latin America, a diagnosis of GCA has been reported amongst Puerto Rican and Mexican people (31) (32). In a case-control study from Mexico, it was noted that the dark featured mestizo population were more commonly affected compared to Mexican people of Caucasian or Spanish ancestry (32). However, a Brazil-based cohort study found that the vast majority of GCA patients in their population were of Caucasian descent (20). These differences amongst Latin American countries illustrate the diversity of ethnic populations within this world region. Given the reported difference in GCA rates between ethnically mixed populations, the

projection of the likely number of people affected by GCA in Africa, Asia, and South America could not be undertaken using available Caucasian incidence rates.

There are some important caveats to our work. Firstly, the UN population and demographic predictions we used to project incidence may prove to be incorrect. In addition, environmental factors, migration and globalization of populations add further complexity to calculating future numbers of GCA worldwide. The studies from which the incidence rates were derived used varying methods to identify and define GCA (Table 1). Some were based on clinical diagnosis alone, whilst others adhered to the ACR classification criteria or histology. The studies identifying GCA by positive TAB only are likely to have underestimated the true incidence rate. GCA cases will have inevitably been missed in some studies and hence our predicted figures will likely be an underestimate of true GCA incident case numbers.

Projecting for countries, where only regional study data is available, does not take into account variation of the incidence rate within that country and may lead to error. This is particularly relevant for countries with many different ethnic groups, such as the USA. In California and Tennessee where there is a larger demographic of Hispanics and African Americans, the incidence rates have been found to be 0.36 per 100,000 and 1.58 per 100,000 respectively (33) (21). For this review, we have used data from the Minnesota study as this is a larger and more frequently repeated study (9). However, Minnesota has a much larger European-derived Caucasian demographic. It is therefore possible that the Minnesota incidence rate is too high to predict GCA for the entire USA population. Projecting for world regions, when only data on a few countries within that region is available, assumes similar incidence rates amongst the other countries for which no data is available. We did not project for world regions which lacked sufficient data.

It is well appreciated that women are more commonly affected than men (34). However, given that only a small number of studies commented on the incidence rate per gender, we were

unable to calculate the sex-specific burden of GCA. Nonetheless, this is not likely to dramatically affect the conclusion of our findings.

The reported number of GCA patients suffering permanent visual loss varies widely. The literature reports incidence for visual loss anywhere from 6% to 70% (35). Both the quoted incidence and the definition of visual impairment vary significantly amongst studies. In addition, information on the degree of visual loss and precise visual defect is often omitted from studies.

We chose to employ a recent figure of 15% rate quoted by Borchers et al in 2012 (1). This rate is consistent with various current global incidence rates reported in other studies (36) (37) (38). The extremely high figures of permanent visual loss from GCA quoted in the earlier literature are probably no longer accurate in view of early recognition of disease and prompt treatment initiation. Evidence now also suggests that with appropriate and early treatment, vision lost amongst GCA patients can improve in approximately 13% of cases (39).

Although different levels of ocular involvement will result in varying degrees of disability and financial burden, there are costs implications with most forms of visual impairment (40). As we were unable to model the costs for the different degrees of visual impairment, we had to make the assumption that all people we predicted to have visual impairment would have some form of permanent visual disability with cost implications. This figure of 15%, although possibly an underestimate of the actual total patient numbers suffering any form of visual impairment, is likely to represent a fairly accurate percentage of patients who will have a substantial visual deficit with resulting visual cost burden.

This study provides an example of the potential cost implications of one steroid-induced side effect: steroid-induced fractures. We were unable to model for all potential complications. This cost should only be viewed as an example and not representative of the total costs of

steroid-induced side effects in GCA. The risks from corticosteroids are dose, duration and patient dependent. Due to lack of data available, we were unable to account for all of these details in our calculations. However, as most patients with GCA will be on corticosteroid treatment for an average of 1-2 years, steroid-induced complications are common and hence critical to factor into our disease burden model.

In summary, GCA as a potentially devastating disease associated with significant visual morbidity and financial burden. To our knowledge this is the first paper projecting the likely future disease burden from GCA on a global scale. The elderly population worldwide is increasing, which will likely cause a greater number of GCA incident cases over time. It is estimated that the total number of cumulative incident cases of GCA across Europe and North America alone will exceed 3 million by 2050. This work highlights the need for further population-based studies to allow for accurate determination of incidence rates. Ongoing research into understanding the mechanisms of disease and alternative avenues for therapeutic intervention is also clearly warranted.

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CONFLICT OF INTEREST STATEMENT:

No author has any competing interests related to this research.

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TABLES

Table 1. Profile of studies reporting annual incidence of 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. (41) (2003)(41)	Norway (North & West)	ACR criteria	1992-1996	32.4
Baldursson et al (42) (1994)	Iceland (Nationwide)	ACR criteria	1984-1990	27.0
Nordborg et al (43) (2003)	Sweden (Göteborg)	Biopsy proven	1976-1995	22.2
Smeeth et al.(44) (2006)	UK (Nationwide)	Clinical criteria	1990-2001	22.0 [†]
Elling et al. (45) (1996)	Denmark (Nationwide)	Biopsy proven	1982-1994	20.4
Kermani et al. (9) (2010)	USA (Minnesota)	ACR criteria	2000-2004	18.9
Gonzalez-Gay et al (46) (2007)	Spain (Lugo)	Biopsy proven	2001-2005	12.9
Abdul-Rahman et al. (38) (2011)	New Zealand (Otago)	Biopsy proven	1996-2005	12.7
Bas-Lando et al (34) (2007)	Israel (Jerusalem)	Biopsy proven or ACR criteria	1980-2004	11.3
Ramstead et al. (47) (2007)	Canada (Saskatoon)	Biopsy proven	1998-2003	9.4
Barrier et al. (48) (1982)	France (Loire-Atlantique)	Biopsy proven or clinical features	1970-1979	9.4 [‡]
Salvarani et al.(49) (1991)	Italy (Reggio Emilia)	Biopsy proven or clinical features	1980-1988	6.9
Dunstan et al. (19) (2013)	Australia (South Australia)	Biopsy proven	1992-2011	3.2
Pamuk et al.(50) (2009)	Turkey (NorthWest)	ACR criteria	2002-2008	1.1

[†] reported for people over age 40 years.

[‡] reported for people over age 55 years.

Abbreviations: ACR, American College of Rheumatology.

Table 2. Regional number of people predicted to be diagnosed with, or sight-impaired due to giant cell arteritis by 2050.

World Region	Countries used in model	<u>Number of people diagnosed</u> Mean (LL - UL)	<u>Number of people visually impaired</u> Mean (LL - UL)
Oceania	Australia & New Zealand	44,229 (17,769 - 70,689)	6,634 (2,665 - 10,603)
North America	Canada & USA	793,836 (527,354 - 1,060,318)	119,075 (79,103 - 159,048)
Europe	France, Norway, Sweden, Iceland, UK, Denmark, Spain, Italy	2,442,274 [†] (794,891 - 3,732,532)	366,341 [†] (119,234 - 559,880)
Total	-	3,280,339 (1,340,014 - 4,863,539)	492,051 (201,002 - 729,531)

[†] calculated as median.

Abbreviations: LL, lower limit; UL, upper limit.

SUPPLEMENTARY TABLES:**Supplementary Table 1.**

Change in incident cases of giant cell arteritis per country and cumulative burden of disease by 2050 in each country.

Country	Proportional increase in incident cases diagnosed in 2015 and 2050 (%)	Predicted Total number of Incident cases by 2050
Australia	169.0	12,488
Canada	147.1	57,840
Denmark	119.9	18,210
France	128.1	98,575
Iceland	167.9	1,418
Israel	196.4	12,082
Italy	118.4	74,770
New Zealand	157.9	9,282
Norway	149.2	26,833
Spain	140.4	107,725
Sweden	130.1	35,007
Turkey	239.7	11,323
UK	134.3	226,097
USA	142.1	943,690
Total	139.7	1,635,341

Supplementary Table 2.

GCA incident cases for each World-Region.

Year	North America	Europe	Oceania
2015	17,643	59,469	866
2020	19,038	62,056	963
2025	20,181	64,323	1,065
2030	21,205	66,291	1,156
2035	22,238	68,205	1,257
2040	23,189	69,628	1,355
2045	24,059	69,420	1,446
2050	24,711	68,027	1,532

Supplementary Table 3.

Financial burden associated with GCA in the USA by 2050.

Complications from GCA	Projected number of people with GCA affected in the USA	Total Costs (US\$)
Visual impairment	141,554	
- Initial inpatient costs	"	\$1,139,364,121
- Ongoing support	"	\$76,291,674,360
Steroid-induced fractures	358,602	\$6,583,183,327