TITLE PAGE

Short running head:

PMR and GCA epidemiology

Full title of manuscript:

Incidence and prevalence of Polymyalgia Rheumatica and Giant Cell Arteritis in a Health Care Management Organization in Buenos Aires, Argentina

Complete given names and surnames of all authors with ORCID ID:

1) José Maximiliano Martínez Perez ORCID ID 0000-0001-7373-3027
2) Florencia Beatriz Mollerach ORCID ID 0000-0002-2292-8139
3) Valeria Scaglioni ORCID ID 0000-0002-1163-7467
4) Facundo Vergara ORCID ID 0000-0002-2570-910X
5) Ignacio Javier Gandino ORCID ID 0000-0003-3540-6169
6) Luis José Catoggio ORCID ID 0000-0002-4047-4863
7) Javier Eduardo Rosa ORCID ID 0000-0003-3331-0761
8) Enrique Roberto Soriano ORCID ID 0000-0003-3143-1084
9) Marina Scolnik ORCID ID 0000-0002-0542-8001

The source(s) of support in the form of grants or industrial support:

This work did not have any contribution or financial recognition from any person or group

Initials, surnames, appointments, and highest academic degrees of all authors (e.g., MD, PhD), and affiliated department(s) and institution(s):

1) J.M. Martínez Perez, MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

2) F.B. Mollerach, MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

3) V. Scaglioni, MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

4) F. Vergara, MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

5) I.J. Gandino, MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

6) L.J. Catoggio, PhD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

7) J. E. Rosa, MSc, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

8) E.R. Soriano MSc, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

9) Marina Scolnik MD, Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina

Conflict of interest:

None related to this manuscript

Corresponding author's name, address, and email:

Marina Scolnik, Peron 4230, Rheumatology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires (C1199ABB), Argentina.

E-mail: marina.scolnik@hospitalitaliano.org.ar

Statement of ethics and consent: This work was approved by the ethics committee of

the Italian Hospital of Buenos Aires (ID: 2752).

Key Indexing Terms (maximum of 6; must be MeSH terms):

Epidemiology; Polymyalgia Rheumatica; Giant Cell Arteritis; Health Services Research; Systemic Vasculitis

ABSTRACT

Objective. To estimate incidence and prevalence of PMR and GCA in a university hospital–based health management organization (HIMCP) in Argentina.

Methods. Overall, and sex-specific incidence rates and prevalence were calculated (age ≥ 50 years). Incidence study followed members with continuous affiliation ≥ 1 year from January 2000 to December 2015. Diagnosis as per the 2012 EULAR/ACR criteria for PMR or the ACR 1990 criteria for GCA. Prevalence was calculated on January 1, 2015.

Results. 176,558 persons contributed a total of 1,046,620 person-years. 825 developed PMR; incidence rate (IR) (per 100,000 person-years) of 78.8 (95% CI 73.4–84.2) overall; 90.1 (95% CI 82.9–97.2) for women, 58.9 (95% CI 51.1–66.6) for men. Ninety persons developed GCA; IR of 8.6 (95%-CI 6.8–10.4) overall; 11.1 (95%-CI 8.5–10.6) for women, 4.2 (2.2–6.3) for men. Prevalent PMR cases: 205 and prevalent GCA cases: 23 were identified from a population of 80,335. Prevalence (Pr) of PMR was 255 per 100,000 (95% CI 220–290) overall, 280 (95% CI 234–325) for women, 209 (95% CI 150–262) for men, and Pr of GCA was 28.6 per 100,000 (95% CI 16.9–40.3) overall, 36.4 (95% CI 20.1–52.8) for women, 14.2 (95% CI 0.3–28.1) for men

Conclusions. This is the first study of incidence and prevalence of PMR and GCA in Argentina. There were similarities and differences with series from other parts of the world, but population based epidemiologic studies in Latin America are needed.

INTRODUCTION

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are inflammatory disorders of unknown etiology that predominantly occur in persons aged 50 years and older(1).

PMR frequency is 3 to 10 times higher than that of GCA; incidence and prevalence is higher in Northern European countries and Nordic countries descendants. Peak of incidence occurs after 60 years of age and the highest peak occurs at 80 years of age (2). Both diseases are more common in females and corticosteroids remain the mainstay of treatment (1–3).

PMR and GCA epidemiological data is scarce in Latin America and in Argentina in particular. The aim of our study was therefore to determine the incidence and prevalence of PMR and GCA in a population belonging to a healthcare program managed by a University Hospital in Ciudad Autónoma de Buenos Aires (CABA), Argentina.

METHODS

The studied populations are people affiliated to a healthcare program provided by a University Hospital (HIMCP) located in Ciudad Autónoma de Buenos Aires (CABA), Argentina. This same population has been studied in epidemiological studies of other diseases where details of their characteristics and similarities to the general population of the CABA can be found (4,5) (see supplementary data, tables 1, 2 and 3).

According to the last census, there were 958343 inhabitants older than 50 years old in CABA in 2010. The great majority of the populations are descendant from white Europeans (6). Although patients with acute or complex chronic diseases are not admitted to the HIMCP, their presence is only screened by a questionnaire, and patients

with common chronic diseases (Type II diabetes, hypertension, dyslipidemia, etc) are admitted.

Incidence Estimation:

Patients were members of the HIMPC, affiliated after the year 2000. They needed to have at least 1-year of affiliation to the healthcare program pre-diagnosis date and to be over 50 years of age. They were followed since affiliation until PMR or GCA were diagnosed, voluntary resignation to the HIMPC, death, or termination of the study (January 1st 2015).

Prevalence Estimation:

For prevalence estimation, the assigned denominator was the number of active members who were over 50 years of age on January 1st 2015 and numerator where those PMR or GCA patients on treatment (receiving corticosteroids or other treatments for those diseases) according to medical records at that time point.

Data Collection:

The data were obtained from the electronic medical records and the following search criteria were established:

1) Database from the rheumatology section (patients included in previous studies); 2) patients with PMR or GCA diagnosis from the hospital´s health problems database, using the following words: polymyalgia rheumatica, giant cell arteritis, temporal arteritis, arteritis, vasculitis, amaurosis fugax, severe headache, jaw claudication; 3) Pharmacy database: patients who purchased more than 3 boxes of meprednisone/prednisone tablets or had purchased them for more than 1 year (one box= 20 8-mg meprednisone

pills); 4) temporal arteritis evidenced by temporal artery biopsy, retrieved from the pathology database.

Erythrocyte sedimentation rate (ESR) (automatized method ALI-FAX), ultra-sensitive C-reactive protein (immunoturbidimetric method), hemoglobin and hematocrit, were collected from the laboratory database.

GCA diagnosis was made by treating physicians based on clinical according symptoms and laboratory data, and the great majority of them confirmed by a temporal artery biopsy and/or temporal doppler ultrasound (available in our hospital since year 2009) performed by an experienced sonographer (showing halo sign). PMR diagnosis was made based on clinical symptoms, laboratory data and confirmed response to low dose of corticosteroids.

All medical records obtained from all different sources were manually reviewed and only patients who were over 50 years of age and fulfilled ACR/EULAR 2012 clinical criteria for PMR and ACR 1990 for GCA were included for incidence and prevalence calculation (7,8) (see supplementary data, Figure 1). If a patient had GCA (fulfilling GCA classification criteria) with PMR symptoms was only counted as a GCA patient.

Statistical Analysis:

All patients diagnosed with GCA or PMR who fulfilled the criteria between the years 2000 and 2015 were included retrospectively.

Incidence rate (IR) was estimated with a 95% confidence interval. IR was calculated for each age group (per decade), considering age at the time of diagnosis for the identified cases and the age at the beginning of the study for the population at risk.

Prevalence was estimated on January 1st 2015 and the denominator assigned was the number of active members over 50 years of age at that time.

Ethical approval

This work was approved by the ethics committee of the Italian Hospital of Buenos Aires (ID: 2752).

Patient consent

When affiliating to the HIMPC, patients give their general consent for using their data in an anonymous way for research purposes. In this study, due to its retrospective and anonymized nature no specific written consent from patients was required by ethics committee.

RESULTS

From the studied population over 50 years of age, 176,558 people contributed a total of 1,046,620 person-years.

Incidence:

Eight hundred twenty-five people were diagnosed with PMR in the study period. The incidence rate was estimated per 100,000 persons-year. The overall rate in the population was 78.8 (95% CI 73.4, 84.2), 90.1 for women (95% CI 82.9, 97.2), and 58.9 for men (95% CI 51.1, 66.6).

Ninety people were diagnosed with GCA with an overall incidence rate of 8.6 persons-year (95% CI 6.8, 10.4), 11.1 for women (95% CI 8.5, 10.6), and 4.2 for men (95% CI 2.2,

6.3).

Prevalence:

On January 1st 2015, 205 PMR prevalent cases and 23 GCA prevalent cases were identified from a denominator population of 80,335 members of the HIMCP. PMR overall prevalence was 255 per 100,000 population (95% CI 220, 290), 280 for women (95% CI 234, 325), and 209 for men (95% CI 150, 262). GCA overall prevalence was 28.6 per 100,000 population (95% CI 16.9, 40.3), 36.4 for women (95% CI 20.1, 52.8), and 14.2 for men (95% CI 0.3, 28.1).

Characteristics of the PMR and GCA populations are shown in table 1. Incidence was higher in females, 73.1% of PMR and 82% of GCA patients; mean age at the time of diagnosis was 75.4 years for PMR and 75.6 years for GCA. The highest incidence peak was at 80 years for PMR and after 70 for GCA (figure 1). PMR prevalence peak was at 70 years of age for females and over 70 for males. For GCA the prevalence peak was at 70 years of age for both sexes (figure 2).

Ninety seven percent of PMR patients suffered from shoulder girdle involvement while 73% of the patients had pelvic pain/stiffness. Thirteen percent of the patients with PMR had arthritis or peripheral tenosynovitis predominantly in hands. Fifty nine percent of the patients with GCA showed PMR symptoms. The most frequent GCA symptom was headache in 78% of the patients, followed by jaw claudication in 54%, and 40% presented some kind of visual alteration, amaurosis fugax and diplopia in 16% and 24%, respectively.

Mean erythrocyte sedimentation rate was 56.7mm/h (SD 25.3) for PMR and 69.8 mm/h (SD 25.1) for GCA at the time of diagnosis.

The median initial meprednisone dose was 8 mg/day (IQR 8-8) for PMR and 40 mg/day (IQR 20-40) for GCA; with a median treatment duration of 20 months (IQR 13-31) for PMR and 29 months (IQR 19-40) for GCA at the end of the study.

DISCUSSION

Our study is the first to provide PMR and GCA epidemiological data in Argentina and one of the first ones to our knowledge in Latin America.

Data published around the world are variable. PMR incidence is high in Nordic countries (9–11), as well as those from Olmsted County, USA (12), where most of the population descends from Northern Europe. One of the highest incidence rates is the one published in the UK, which was 84.2/100,000 person-years in the period between 1990 and 2001 (13). In contrast, in Southern European countries incidence is low around 22/100,000 person-years (14). In a recent review of the epidemiology of PMR in Italy an incidence between 12 and 23 cases/100,000 inhabitants were reported (15).

Incidence in our population was higher: 78.8/100,000 person-years (95% CI 73.4, 84.2), but within the range of rates reported in a recent systematic review, and close to the figures reported in UK and USA (16).

Regarding Latin America, in Colombia, a PMR prevalence was reported of 200/100,000 habitants over 50 years old (17), results that are very similar to our data (255/100,000).

There are several differences between the different studies that might explain different results; such as the criteria used for diagnosis (some studies used Bird's or Healey's criteria others the ACR criteria, and others physician diagnosis), the use of normal ESR as exclusion criteria (as in one of the Italian studies), different cut off values for ESR as

inclusion criteria, and also different populations included (patients diagnosed by general practitioners, or referred to rheumatology centers, population based, etc). With all these differences among studies it is difficult to draw a conclusion on which ones are the more accurate figures. We took a population-based approach, although our population might have some special characteristics that are not necessarily generalizable, as discussed below.

In a recently published metanalysis that included 107 studies the pooled incidence of GCA was 10.00 [9.22, 10.78] cases per 100,000 people over 50 years old (18). The incidence was highest in Scandinavia: 21.57 [18.90, 24.23], followed by North and South America 10.89 [8.78, 13.00], Europe 7.26 [6.05, 8.47], and Oceania 7.85 [− 1.48, 17.19]. These figures are like what we found in our study. Pooled prevalence in that metanalysis was 51.74 [42.04, 61.43] cases per 100,000 people over age 50 (18). Our prevalence was within that range, lower than the one reported in Denmark, Italy, USA and Germany, and higher than Tunisia, Japan, Turkey and Spain. As in PMR several factors might explain the differences, such as the lack of standardized definition for GCA, in particular when administrative databases are used, as there are no specific billing codes for GCA; inconsistency in the inclusion criteria used, where the majority of hospital-based studies included only biopsy-proven cases, whereas most population or community-based studies (such as ours) included also clinical diagnoses. Also, most studies on prevalence included cases with GCA or PMR with a past diagnosis who were alive and living in the study area at the time of the study (16), and as we think that a patient who has stopped all treatment and has no symptoms does not have prevalent disease, we did not include those patients and that might explain our lower prevalence.

This work has several limitations. One is due to the fact that the HIMCP is a medical care plan that does not incorporate "sick" patients. Therefore, our prevalent cases could be reduced because people with either disease would not have been allowed into the plan. Although this limitation would affect prevalence and would not affect incidence, it is possible that PMR or GCA are more often diagnosed in healthy people rather than in patients with multiple comorbidities. It is also possible that healthier patients receive corticosteroids for extended periods of time (we usually are more concerned about steroids use in patients with multiple co-morbidities), and that bias could affect prevalence.

Another limitation is the generalizability. Although the population of the HIMCP is similar in age and economic distribution to the overall population of CABA (see supplementary data), we have to be cautious with considering this valid for the whole city. Even more, to the rest of the country. However, they are the first results published in Argentina and may be useful for future comparisons.

Another difficulty is GCA definition. As we currently know, GCA is a more complex disease affecting not only cranial arteries but also large vessels, mainly thoracic. In this study and almost every study published around the world, GCA epidemiology mainly takes into account cranial disease, since large vessel involvement is not easily recognized nor registered, so underestimating true incidence and prevalence of the disease.

We did not investigate whether patients with GCA and PMR symptoms fulfilled also PMR classification criteria and we have classified them as GCA only. In our cohort there were 53 patients with incident GCA and PMR symptoms (table 1). In the case that these patients would have fulfilled PMR classification criteria and we have counted them as

having incident PMR, PMR incidence rate would have been 83.9/100,000 person-years, a little bit higher that the one we are reporting but within the 95% confidence interval. In these cases where both entities coexist, GCA diagnosis is the one that is going to lead treatment decisions and that is why we have classified them like this, but we do recognize that it can be another study limitation.

Differences and similarities in incidence and prevalence with series from other parts of the world are difficult to explain. True genetic and environmental differences may be in part confounded by referrals bias and case definitions, particularly for GCA.

This is the first GCA epidemiological study published from Latin America and one of the first ones showing epidemiological PMR data of this region. We know that our population is different from other sites of the world, and having appropriate data may allow us to have a better understanding of diseases and to plan a proper medical care of these patients. Clearly population-based epidemiology studies are needed in Latin America.

REFERENCES

1. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA 2016;315:2442-58.

2. Mahr A, Aouba A, Richebé P, Gonzalez-Chiappe S. Epidemiology and natural history of giant cell arteritis. La Rev Med interne 2017;38:663-9.

3. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11:229.

4. Di WT, Vergara F, Bertiller E, Gallardo M de LA, Gandino I, Scolnik M, et al. Incidence and Prevalence of Rheumatoid Arthritis in a Health Management Organization in Argentina: A 15-year Study. J Rheumatol 2016;43:1306-11.

5. Soriano ER, Rosa J, Velozo E, Schpilberg M, Imamura PM, Diaz J, et al. Incidence and prevalence of psoriatic arthritis in Buenos Aires, Argentina: a 6-year health management organization-based study. Rheumatology 2011;50:729-34.

6. INDEC: Instituto Nacional de Estadística y Censos de la República Argentina [Internet]. [cited 2022 Jan 16]. Available from: https://www.indec.gob.ar/indec/web/Nivel4-CensoProvincia-999-999-02-999-2010

7. Dasgupta B, Cimmino MA, Kremers HM, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum 2012;64:943-54.

8. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.

9. Boesen P, Sørensen SF. Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a Danish county. A prospective investigation, 1982-1985. Arthritis Rheum 1987;30:294-9.

10. Schaufelberger C, Bengtsson BA, Andersson R. Epidemiology and mortality in 220 patients with polymyalgia rheumatica. Br J Rheumatol 1995;34:261-4.

11. Gran JT, Myklebust G. The incidence of polymyalgia rheumatica and temporal arteritis in the county of Aust Agder, south Norway: a prospective study 1987-94. J Rheumatol J Rheumatol; 1997;24:1739-43.

12. Raheel S, Shbeeb I, Crowson CS, Matteson EL. Epidemiology of Polymyalgia Rheumatica 2000-2014 and Examination of Incidence and Survival Trends Over 45 Years: A Population-Based Study. Arthritis Care Res (Hoboken) 2017;69:1282-5.

13. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. Ann Rheum Dis 2006;65:1093-8.

14. De Socio A, Perrotta FM, Grasso GM, Lubrano E. Incidence of rheumatoid arthritis, psoriatic arthritis and polymyalgia rheumatica in an inland area of central Italy: results of the CAMPO-RHE study. Postgrad Med 2018;130:137-41.

15. Manzo C. Incidence and Prevalence of Polymyalgia Rheumatica (PMR): The Importance of the Epidemiological Context. The Italian Case. Med Sci ; 2019;7:92.

16. Sharma A, Mohammad A, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: A systematic literature review. Semin Arthritis Rheum Semin Arthritis Rheum; 2020;50:1040-8.

17. Fernández-Ávila DG, Bernal-Macías S, Rincón-Riaño DN, Gutiérrez JM, Rosselli D. Prevalence of polymyalgia rheumatica in Colombia: data from the national health registry 2012-2016. Rheumatol Int Rheumatol Int; 2019;39:1631-5.

18. Li KJ, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. Arthritis Res Ther Arthritis Res Ther; 2021;23.

Figure 1. PMR and GCA incidence rates, by sex and age

Figure 2. PMR and GCA prevalence, by sex and age

Table 1. Patients characteristics at onset disease (incident cases)		
Variables	**PMR (n=825)**	**GCA (n=90)**
Females, n (%)	603 (73.1)	74 (82.2)
Mean age at diagnosis, years (SD)	75.4 (7.9)	75.6 (11.1)
Bilateral shoulder aching, n (%)	798 (96.7)	-
Bilateral pelvic girdle (hip) aching, n (%)	602 (72.9)	-
Peripheral synovitis (distal swelling, tenosynovitis or arthritis), n (%)	107 (12.9)	-
PMR symptoms, n (%)	825 (100)	53 (58.9)
Elevated erythrocyte sedimentation rate, n (%)	700 (84.8)	87 (96.7)
Mean erythrocyte sedimentation rate (SD)	56.7 (25.3)	69.8 (25.1)
Median meprednisone initial dose, mg (IQR)	8 (8-8)	40 (20-40)
Median months on steroid treatment (IQR)	20 (13-31)	29 (19-40)
Jaw claudication, n (%)	-	48 (53.3)
Headaches, n (%)	-	70 (77.8)
Visual impairment, n (%)	-	36 (40.0)

PMR: polymyalgia rheumatica; GCA: giant cell arteritis; SD: standard deviation; IQR: interquartile range