


Whole-Country and Regional Incidences of Giant Cell Arteritis in French Continental and Overseas Territories: A 7-Year Nationwide Database Analysis

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Objective. The incidence rate of giant cell arteritis (GCA) is poorly studied in France. Therefore, we conducted a national hospital database study to assess the overall and regional incidence rates of GCA in France, including overseas territories.

Methods. Through the national hospitalization database of all patients hospitalized in France, new incidental GCA was identified using *International Classification of Diseases, 10th Revision* medical codes (M31.5 = GCA; M31.6 = GCA and polymyalgia rheumatica [PMR]) during 2013–2019. The regional incidences were analyzed by graphical methods and Poisson regression.

Results. A total of 16,540 new GCA with or without PMR diagnoses were identified in all French hospitals over 7 years. The female/male ratio was 1.8. The crude annual incidence rate of GCA with or without PMR was 9.64 (9.50–9.79) per 100,000 persons aged 50 years or older in continental France and 2.91 (2.35–3.47) in overseas areas. The GCA with or without PMR incidence rate regularly increased with age in both sexes but with a later peak in men (85 vs 80 years in women). The crude incidence rate was 11.43 (11.21–11.65) in women and 7.50 (7.31–7.70) in men. An east–western gradient was noted with an increasing standardized incident rate (SIR) from east to west ($P < 10^{-3}$) using a departmental stratification of incident rates. Of note, all SIRs in continental regions were higher than those in overseas areas.

Conclusion. This French nationwide study provides new and dynamic insights regarding GCA with or without PMR incident rates at the country and regional levels. Important rate differences were observed between continental France and the overseas areas.

INTRODUCTION

Giant cell arteritis (GCA) is the most frequent systemic vasculitis in patients older than 50 and more commonly affects women (1). The external carotid artery branches' typical involvement explains cranial symptoms, such as temporal headaches, jaw claudication, scalp tenderness, or ophthalmologic signs. The aorta and its branches can be affected in 40% of patients, most often without subsequent symptoms. GCA is associated with polymyalgia rheumatica (PMR) in one third to half of the patients. Most often, the diagnosis of GCA relies on suggestive clinical symptoms, increased

acute phase reactants, and vasculitis demonstration on temporal arteries or large-vessel imaging (1,2). Currently, most patients in France with suspected GCA are referred to a hospital through a fast-track process to undergo vascular workup, such as a temporal artery biopsy, temporal artery ultrasonography, or large-vessel imaging, as well as an ophthalmological examination if necessary.

Over the last decades, epidemiologic studies of GCA have indicated that geographical gradients exist, mainly a north–south decreasing gradient, with a higher incidence of the disease in populations from northern countries, especially in Scandinavian countries (21–30 cases per 100,000 persons older than 50 years

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old), followed by North America (11 per 100,000 people older than 50 years old) (3). There also probably exists at a worldwide level a west–east decreasing gradient because GCA appears very rarely in Asian populations (4,5). Some studies conducted in Asia or the United States provided significant differences in GCA frequency according to the patients' ethnic origins. Compared with patients of White origin, those of African American or Asian origin were five to seven times and 20 times less affected, respectively (5–7). The immunogenetic background probably participates in the susceptibility of developing GCA because different genetic associations were observed according to the patients' origins. The HLA–DRB1*04 allele (often DRB1*0401 and DRB1*0404) is the best-established susceptibility factor in GCA (8–13).

In Europe, excluding Scandinavian countries, a recent meta-analysis indicated a pooled incidence of 7.26 per 100,000 people older than 50 (3). Few epidemiologic data are available in France. Barrier et al (14) found an incidence rate of 10 per 100,000 people of the general population over a 10-year period (1970–1979) in a single French West department (Loire-Atlantique). More recently, using the GCA medical code in a 1% sample of the French national health insurance system, Mahr et al (15) found 241 incident cases between 2007 and 2015, reflecting an annual incidence of 7 to 10 per 100,000 people older than 50 years old. These two studies were thus limited because the analysis only focused on 1 of the 101 French departments or only analyzed a very small sample of the population.

France might be an interesting model to analyse the influence of the immunogenetic background on GCA incidence rates. Over the last centuries, under the pressure of natural selection processes, genetic recombination and mutations, and migration flows, the distribution and frequency of candidate genes differed within populations and territories. The French territory has always been subject to the secular reception of migratory populations for other continents, including mostly North and Sub-Saharan Africa, with probably different latitudinal, longitudinal, or regional and/or departmental distributions. As an example, the different immunogenetic backgrounds of the French population are especially emphasized when comparing continental and overseas populations. In addition, historically, some metropolitan territories from northwestern France, including the Normandy region (ie, etymologically northern man), have been conquered and occupied by Viking populations coming from the actual Scandinavian territories, where the prevalence and incidence of the disease is currently recognized as the highest.

In this study, we used a nationwide database of hospitalizations to estimate the overall incidence of GCA in France. In parallel, we aimed to analyse whether gradual geographical and dynamic differences might be observed in continental and overseas France and at a departmental level.

PATIENTS AND METHODS

Patients selection. In this nationwide cohort study, patients were retrieved from the national hospitalization database

(Programme de Médicalisation des Systèmes d'Information [PMSI]), which systematically includes administrative and medical information regarding all patients hospitalized in France. Additional information on the PMSI is available as Supplementary Material. Within the database, medical diagnoses are coded using the *International Classification of Diseases, 10th Revision*. Technical procedures performed during hospitalization, such as temporal artery biopsy (TAB), are also noted. Our hospital has authorized access to the data from the PMSI (CNIL [Commission Nationale de l'Informatique et des Libertés]: No. 2217578 v0).

Patients were identified in the PMSI database using the main and associated codes M31.5 (GCA) and M31.6 (GCA with PMR). The main diagnosis code is defined as the reason for hospitalization, whereas the associated diagnostic code is comorbidities or complications detected or treated during hospitalization. To capture the incidence rate of GCA with or without PMR, we retrieved only the first hospitalization stay where GCA with or without PMR was mentioned as the main diagnosis. If GCA with or without PMR was noted as an associated code, we only retained this occurrence as an incident case if a TAB (code EBHA001) was performed or a histopathological analysis of a temporal artery was coded (code ENQX011) during the hospitalization stay. Given the absence of a PMSI code for the diagnosis of vasculitis evidenced on imaging, patients diagnosed with GCA on the basis of the results of vascular imaging were not included.

Data from the PMSI from 2011 to 2019 were used to identify the first hospitalization corresponding to inclusion criteria. The first 2 years (2011 and 2012) were only used to ensure a minimal time period of 2 years before the incident hospitalization for all patients to exclude relapses. The study period was from January 2013 to December 2019. No patient with a GCA with or without PMR diagnosis in 2013 or beyond was hospitalized with this code in the previous years, limiting the risk of including GCA relapses.

We excluded patients aged less than 50 years at the time of diagnosis and those residing outside France.

Studied parameters. Data extracted from the PMSI database included age, sex, month and year of diagnosis, and department and region where the diagnosis was made.

We collected the number of cases from the study period and separately analyzed the repartition between men and women as well as between different age groups (50–59, 60–69, 70–79 and ≥ 80).

Incident rates were calculated at the continental France level, the regional and departmental levels, and the main French overseas area level (Guadeloupe, Martinique, and La Réunion). We distinguished crude incident rates when the denominator was the population 50 years and older in the country, region, or department analyzed and standardized incident rates (SIRs) using the mean age and sex distribution of the 2013–2019 continental French population 50 years and older as the reference.

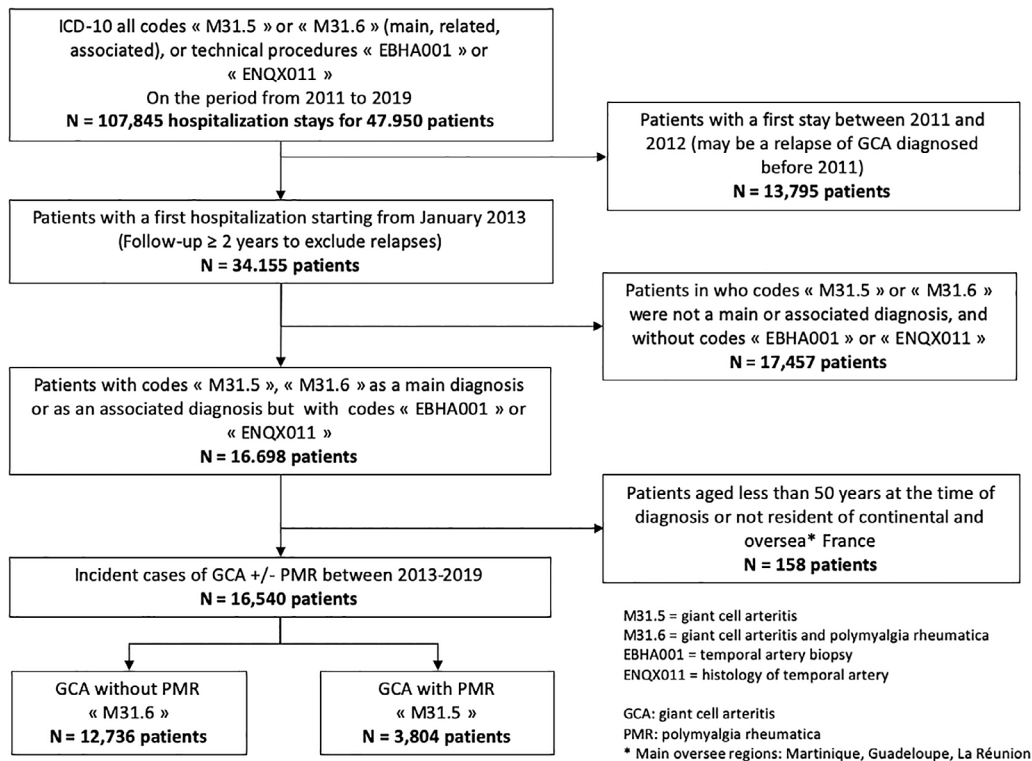


Figure 1. Flowchart of the patients' selection. GCA, giant cell arteritis; ICD, *International Classification Of Diseases, 10th Revision*; PMR, polymyalgia rheumatica.

A geographical gradient in continental France was searched by analyzing a potential trend of incident rates using the center point of 97 different departments.

Statistical analyses. Data about the population came from the French National Institute of Statistics and Economic

Studies database and were obtained via the Technical Agency of Information About Hospitalization.

Each department center point was calculated using latitude and longitude coordinate pairs and expressed in decimal degrees (DDs). An increase in latitude in DD corresponds to an east move, whereas an increase in longitude in DD corresponds to a north move. We calculated geographical gradients of incident rates

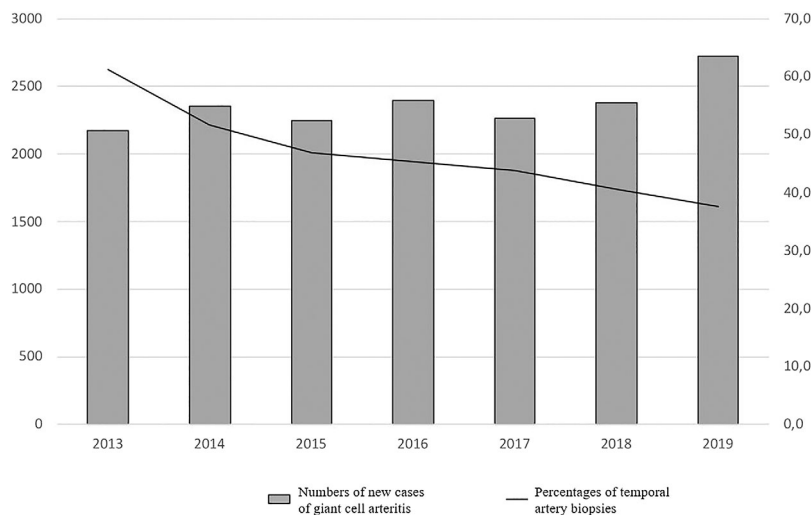


Figure 2. Annual incidence rates of giant cell arteritis between 2013 and 2019 and evolution of the rates of temporal artery biopsies performed to diagnose giant cell arteritis in the same period.

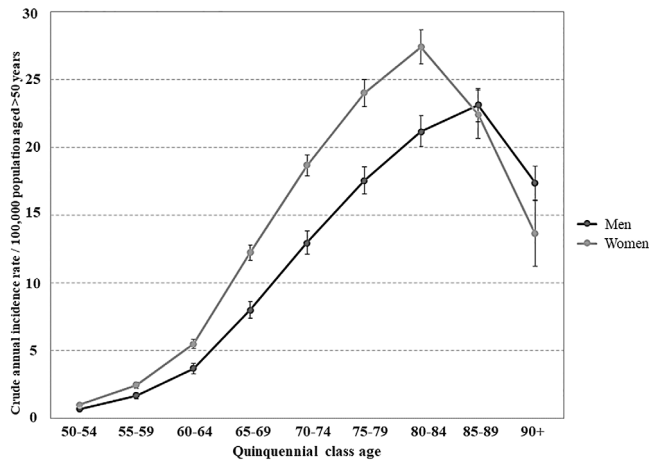


Figure 3. Incidence rates of giant cell arteritis with or without polymyalgia rheumatica in both sexes according to a quinquennial class age distinction in continental France.

adjusted for age and sex using Poisson regression, considering overdispersions.

Statistical analyses were computed using SAS Enterprise Guide software (8.3 version; SAS Institute, Inc). A *P* value less than 0.05 was considered significant.

RESULTS

From 2013 to 2019, 16,540 patients were newly diagnosed with GCA with or without PMR through hospital recruitment in French territory, of whom 16,436 were detected in continental France and 104 in overseas areas. Figure 1 shows the flowchart of patients' selection.

A mean of 2363 (range: 2170-2722) new GCA diagnoses were made each year in France. Sixty-five percent of patients were women. The age repartition was as follows: 5.2% of patients with GCA were between 50 and 59 years old, 22.1% were between 60 and 69, 37.3% were between 70 and 79, and 35.5% were older than 80.

Incidence rates did not significantly vary each year during the study period; however, the use of a TAB to diagnose GCA significantly decreased, from 61% in 2013 to 38% in 2019 ($P < 0.0001$; Figure 2).

The crude incidence rates of GCA with or without PMR per 100,000 persons aged 50 years and older were 9.64 (9.50-9.79) in continental France and 2.91 (2.35-3.47) in overseas areas. The crude incidence rate was 11.43 (11.21-11.65) in women and 7.50 (7.31-7.70) in men ($P < 0.0001$). Figure 3 shows that the incidence rate of GCA with or without PMR increased with

Table 1. Standardized incidence rates of GCA in the 13 main and 22 historical regions in continental France

Main regions	Historical regions	Map identification (Figure 4B)	Standardized incidence rates ^a (CI)
Auvergne Rhône Alpes			11.74 (11.26-12.21)
	Auvergne	1	12.11 (11.06-13.16)
	Rhône Alpes	2	11.65 (11.12-12.18)
Bourgogne Franche-Comté			9.18 (8.52-9.83)
	Bourgogne	3	9.71 (8.86-10.57)
	Franche-Comté	4	8.33 (7.32-9.33)
Bretagne	Bretagne	5	10.60 (9.94-11.26)
Centre Val de Loire	Centre	6	9.17 (8.48-9.86)
Corse	Corse	7	7.01 (5.32-8.69)
Grand Est			8.77 (8.29-9.26)
	Alsace	8	9.17 (8.29-10.06)
	Champagne-Ardenne	9	9.91 (8.88-10.94)
	Lorraine	10	7.82 (7.12-8.52)
Hauts de France			8.92 (8.43-9.42)
	Nord Pas de Calais	11	9.55 (8.92-10.19)
	Picardie	12	7.70 (6.90-8.50)
Ile de France	Ile de France	13	10.65 (10.23-11.07)
Normandie			9.72 (9.08-10.37)
	Basse Normandie	14	9.46 (8.55-10.37)
	Haute Normandie	15	10.01 (9.10-10.92)
Nouvelle Aquitaine			9.96 (9.50-10.42)
	Aquitaine	16	9.92 (9.30-10.55)
	Limousin	17	10.22 (8.98-11.47)
	Poitou-Charentes	18	9.90 (9.08-10.73)
Occitanie			9.52 (9.05-9.99)
	Languedoc-Roussillon	19	9.14 (8.48-9.80)
	Midi-Pyrénées	20	9.89 (9.22-10.56)
Pays de la Loire	Pays de la Loire	21	11.06 (10.40-11.72)
Provence Alpes Côte d'Azur	Provence Alpes Côte d'Azur	22	8.25 (7.78-8.71)

Abbreviations: CI, confidence interval; GCA, giant cell arteritis.

^aPer 100,000 persons aged ≥50 years, standardized on the national population of continental France.

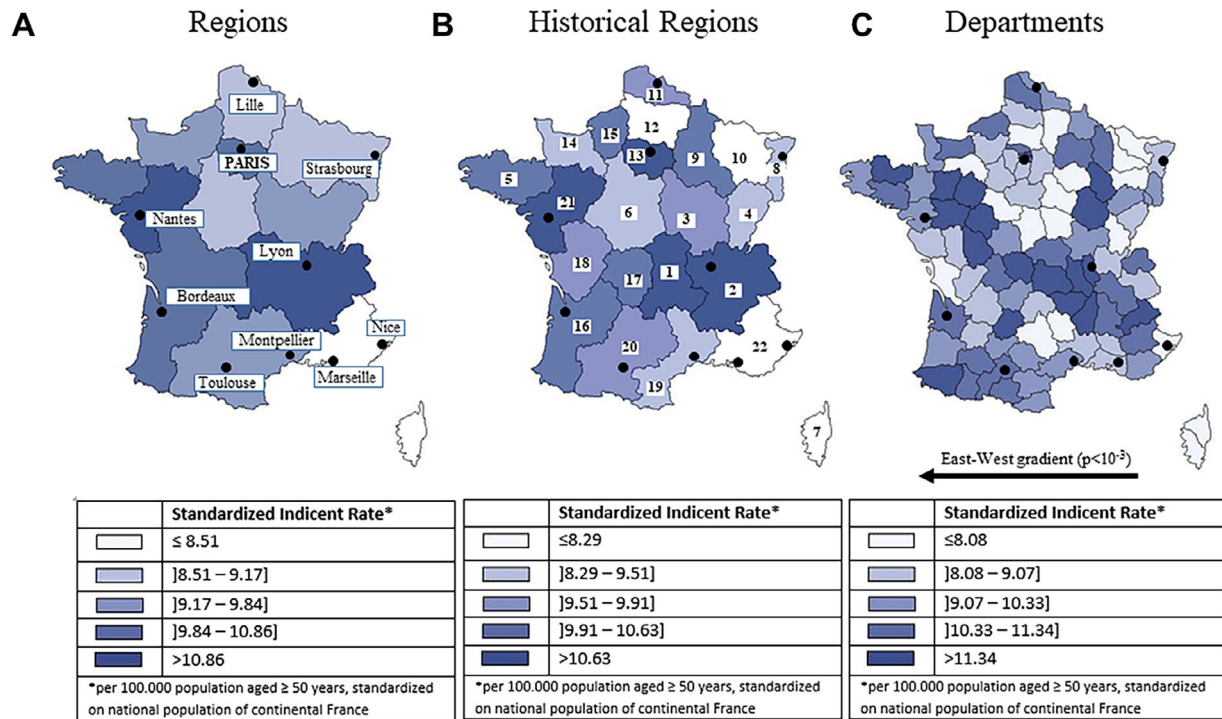


Figure 4. Standardized incident rates of giant cell arteritis with or without polymyalgia rheumatica in the 13 new main regions (A), in the 22 former regions (B), and in the 97 continental (including Corsica) departments (C). Numbers on B refer to the French historical regions described in Table 1.

age, from 50 to 54 to 80 to 85 years old in women and from 50 to 54 to 85 to 89 in men. It decreased in both sexes thereafter.

The detailed SIRs of GCA with or without PMR in the recently reformed 13 and 22 old continental French regions are shown in Table 1 and Figure 4A and B. In overseas areas, the SIR of GCA with or without PMR was 3.45 (2.77-4.12).

At a departmental level, detailed in Figure 4C, a gradient was noted with increasing SIRs from east to west ($\beta = -0.016 [-0.023 \text{ to } -0.009]$, $P < 10^{-3}$). No significant north-south gradient was observed.

DISCUSSION

Available information on GCA incidence in France only relies on cross-sectional studies of small continental population samples or dates before 1990, which no longer are representative of the overall French population (14,15). In this longitudinal and dynamic study gathering data over a 7-year period through a whole French hospitalization-based cohort, we provided a nationwide incidence of 9.64 (9.50-9.79) cases per 100,000 persons aged 50 years and older, which concurs with previous local estimations (14,15). In addition to the known female predominance of the disease, this study shows different age-related curves of GCA distribution in both sexes, with a later peak age incidence rate in men than in women at 85 and 80 years old, respectively.

Until a few years, histological evidence of vasculitis was required to formally diagnose GCA, explaining the frequent

performance of a TAB. In our study period, we observed a decreasing rate over time of TAB performance, which is probably explained by the more frequent use of vascular imaging to demonstrate vasculitis (16-18). As evidence, recent prospective studies in GCA included patients with vasculitis demonstration on imaging, which was never observed in studies before 2015 (19).

Mostly, rather than a south-north increasing gradient, this study identified two socioepidemiologic and ethnodemographic points in GCA. First, we observed an increasing east-western gradient of GCA within continental France at a departmental level. Second, we observed highly heterogeneous SIRs, varying almost twofold in French continental areas (from 7 to 12 cases per 100,000 persons aged ≥50 years). They were at least twofold to fourfold higher than SIRs observed in overseas areas (3 per 100,000 persons aged ≥50 years), where the population is mostly of African origin.

Because of standardization, the differences in SIRs cannot be attributed to age differences. Two main hypotheses can be stated to explain the geographical variations of incidence observed. First, the hospital diagnosis of GCA depends on access to the health care system. This could explain the smaller SIRs observed in some rural regions of central France. However, in France, the care costs for GCA and PMR are fully covered by the national health security system. Thus, the potential lower access to the health care system probably does not rely on financial considerations but on geographical distance from any

medical structure. Second, dynamic genetic factors related to ethnic and/or ancestry origins are also probably involved. In France, ethnic-based statistics are not legally authorized. On the one hand, century-old migratory flows, especially from the Viking invasions from northern Europe, which exhibits the highest GCA incidence, probably partly explain the dynamic and the current moderately higher incidences of GCA observed in the most western geographical areas in France (3,20,21). On the other hand, more recent historical and contemporary movements of Maghreb and Sub-Saharan African populations, which exhibit lower GCA incidence (7), and mostly initially settled down in some south French great towns or regions, probably participate in the lower incidences observed in some of these geographical areas. In the future, because of the dynamism of modern socioeconomic factors, these demographic pictures will probably continue to change.

A recent meta-analysis pooled 107 epidemiological studies worldwide and found a global incidence of GCA of 10.00 (9.22-10.78) cases per 100,000 persons older than 50 years old (3). This study confirms the existence of a latitude gradient, with the highest incidence observed in Scandinavian countries (21.57 [18.80-24.23] cases per 100,000 persons older than 50 years old). In contrast, pooled data from European countries showed an incidence of 7.29 (6.05-8.47) cases per 100,000 persons older than 50 years old. In our study, at the level of a southwest European country, we did not observe some latitude gradient among the different departments. Instead, we found a longitudinal gradient, with increasing rates toward the western continental departments.

Although our study is the first to determine the GCA incidence rate through a large-scale analysis, some limitations should be acknowledged. The incidence rates we provided are probably underestimated, but only slightly, for two reasons. First, the database we used only included new GCA diagnoses made through hospital recruitment. Therefore, the patients diagnosed in community settings were not captured in this study. However, GCA remains mainly and has become increasingly diagnosed at hospitals or referred at least at day hospitals, especially with the development of fast-track pathways, including a multidisciplinary approach. In addition, the PMSI database does not include visits to the emergency department that were not followed by an admission into a regular ward. However, a possible admission to the emergency department does not change the overall trajectory of patients with suspected GCA. Indeed, patients with suspected GCA admitted to the emergency department are often examined before discharge by a GCA specialist. When the diagnosis is established or highly credible, these patients return home with a treatment and a schedule for early additional workup in a day hospital or conventional hospitalization unit (captured within the PMSI).

Second, the methodology we used captured patients hospitalized for GCA that was coded as the main diagnosis. However,

patients whose GCA was an associated diagnosis were also registered in the database if a TAB or histology was obtained during the hospital stay. On the other hand, because TAB is losing favor to vascular imaging and given the absence of specific codes for this type of imaging, we missed some patients with imaging-based GCA diagnoses and no ulterior hospital stay dedicated to GCA treatment or exploration.

Although it cannot be ruled out that there were coding errors in PMSI recordings, there would be no underlying geographical gradient for these errors.

Finally, only 23% of patients presented concomitant PMR, which is probably underestimated and related to imprecise coding. Indeed, there are two codes for GCA (M31.5 for GCA and M31.6 for GCA with PMR). Given the absence of any difference regarding payback whether or not PMR is selected, physicians might have selected the first available code or the more serious condition, ie, M31.5.

To conclude, this large-scale study provides up-to-date and detailed credible data on the overall and regional incidence rates of GCA in France. The results led to a discussion on the contemporary and historical sociodemographic movements that might influence the disparities observed within continental and overseas France. This study identified a west–east decreasing gradient in GCA incidence rates in continental territories. At a European level, these data confirm the north–south decreasing gradient, with a lower GCA incidence rate in France than in Scandinavian countries. At a worldwide level, our data also reinforce an overview of the lower incidence rate of GCA in populations of African origin, as found in French overseas areas. Comparable nationwide database studies and international prospective epidemiological studies, including those conducted in countries authorizing ethnic statistics, should help to refine best the demographic and genetic factors involved in GCA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Aouba had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Guittet, de Boysson, Aouba.

Acquisition of data. Guittet.

Analysis and interpretation of data. Guittet, de Boysson, Cerasuolo, Morello, Sultan, Deshayes, Aouba.

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