Autoimmunity Reviews 22 (2023) 103341

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Increased incidence of giant cell arteritis and associated stroke during the COVID-19 pandemic in Spain: A nation-wide population study

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ARTICLE INFO

Keywords:
Giant cell arteritis
Stroke
COVID-19
SARS-CoV-2 vaccine

ABSTRACT

Introduction: SARS-CoV-2 infection and COVID-19 vaccines might have increased the incidence of giant-cell arteritis (GCA) and the risk of associated stroke in Spain.

Methods: Retrospective nation-wide observational analysis of all adults hospitalized with GCA in Spain during 5 years (Jan-2016 and Dec-2021). The incidence and proportion of admissions with or because of GCA and GCA-associated stroke were compared between pre-pandemic (2016–2019) and pandemic (2020 and 2021) years. Sensitivity analyses were conducted for the different COVID-19 waves and vaccine timing schedules.

Results: A total of 17,268 hospital admissions in patients diagnosed with GCA were identified. During 2020 there were 79.3 and 8.1 per 100,000 admissions of GCA and GCA-associated stroke, respectively. During 2021 these figures were 80.8 and 7.7 per 100,00 admissions, respectively. As comparison, yearly admissions due to GCA and GCA-associated stroke were 72.4 and 5.7 per 100,00, respectively, during the pre-pandemic period ($p < 0.05$). Coincident with the third wave of COVID-19 (and first vaccine dosing), the rate of GCA-associated stroke admissions increased significantly (from 6.7 to 12%; $p < 0.001$). Likewise, there was an increase in GCA-associated stroke (6.6% vs 4.1%, $p = 0.016$) coincident with the third dose vaccination (booster) in patients older than 70 at the end of 2021. In multivariate analysis, only patients admitted during the third COVID-19 wave (and first vaccine dosing) (OR = 1.89, 95% CI 1.22–2.93), and during the third vaccination dosing in patients older than 70 (booster) (OR = 1.66, CI 1.11–2.49), presented a higher GCA-associated stroke risk than the same months of previous years after adjustment by age, sex, classical cardiovascular risk factors and COVID-19 diagnosis.

Conclusions: The COVID-19 pandemic led to an increased incidence of GCA during 2020 and 2021. Moreover, the risk of associated stroke significantly risen accompanying times of COVID-19 vaccine dosing, hypothetically linked to an increased thrombotic risk of mRNA-SARS-CoV-2 vaccines. Hence, forthcoming vaccine policies and indications must weigh the risk of severe COVID-19 with the risk of flare or stroke in patients with GCA.

Abbreviations: AION, Anterior ischemic optic neuropathy; CI, Confidence interval; CRF, Cardiovascular risk factors; GCA, Giant cell arteritis; ICD, International Classification of Diseases; ICU, Intensive care Unit; SNHDD, Spanish Hospital Discharge Database; TIA, transient ischemic attack.

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https://doi.org/10.1016/j.autrev.2023.103341
Received 26 March 2023; Accepted 13 April 2023
Available online 14 April 2023

1. Introduction

Giant-cell arteritis (GCA) is a chronic granulomatous vasculitis involving large and medium sized arteries [1]. Although GCA can potentially occur any time after 50 years of age, the disease typically affects elderly patients, with the peak incidence being between 70 and 80 years [2,3]. Clinically, GCA usually presents with an insidious course with general manifestations including fever, asthenia or weight-loss, along with local symptoms due to arterial inflammation and vascular deficits such as headache or jaw claudication [2]. When the arterial compromise is severe enough, GCA might lead to ischemic phenomena, such as acute ischemic optic neuropathy (AION), transient ischemic attack (TIA) or even established stroke, frequently in the carotid or vertebrobasilar territories [3,4]. These severe complications can occur in up to 20–50% of patients with GCA and usually appear within the period of active disease [4]. GCA pathogenesis is yet practically unknown [5]. However, some reports have pointed out the potential role of certain viruses, such as cytomegalovirus or varicella zoster, as well as influenza vaccines, as triggers for GCA in predisposed individuals [6–8].

The surge of SARS-CoV-2 infection by the end of 2019 in China and its rapid spread worldwide is an unprecedented medical phenomenon. Millions of deaths have occurred during the three years since the pandemic onset [9]. However, COVID-19 is clinically very heterogeneous [10]. On the one hand, a majority of patients present an asymptomatic or oligo-symptomatic illness whilst other might suffer an interstitial pneumonia and even an acute respiratory distress syndrome (ARDS), the main cause of death in these patients. In addition, a subset of patients develops what has been called a 'cytokine storm', a syndrome of systemic hyperinflammatory dysregulation with coagulation disorders, thromboembolic events, myocarditis, acute kidney injury, hepatitis and multi-organ failure [11]. The cytokine storm has been compared to catastrophic antiphospholipid syndrome (CAPS), Still's disease or hemophagocytic lymphohistiocytosis, all severe hyperinflammatory conditions strongly associated with autoimmunity [12]. Altogether, the similarities between severe COVID-19 and certain autoimmune diseases could explain why both SARS-CoV2 infection and COVID-19 vaccines have been related to autoimmune disease onset, disease flares and more severe inflammatory activity during the pandemic [13–15]. Indeed, small-size and/or monocenter reports have claimed an increase of cases of GCA and/or associated ischemic events following COVID-19 disease and/or vaccination, although this observation has not been confirmed by others [16–30].

In the light of the aforementioned considerations, the aim of the present study was to assess the impact of COVID-19 pandemic and SARS-CoV-2 vaccines on the incidence of GCA and the development of GCA-associated stroke in a nation-wide analysis conducted in Spain, a 47 million population country.

2. Methods

2.1. Study population

We performed an analysis of data extracted from the Spanish Hospital Discharge Database (SNHDD), a registry belonging to the Spanish Ministry of Health. The SNHDD includes demographic and epidemiological data and up to 20 discharge diagnoses carried out during admission and defined by the International Classification of Diseases (ICD-10) from January 1st, 2016. We selected hospital admissions from 2016 to 2021 for patients with a diagnosis within the ICD-10 code M31.5 (giant cell arteritis with polymyalgia rheumatica) and M31.6 (other giant cell arteritis) at any position in the list. The study complies with the Declaration of Helsinki and was approved by the local research ethics committee (PI 68–23). The database was provided after all potential patient identifiers were deleted ensuring the anonymity of data.

2.2. Definitions, variables and outcomes

Demographics and outcome data, including age, sex, ethnicity, length of admission, intensive care unit (ICU) admission or in-hospital mortality was retrieved from the database. Besides, considering that the main diagnosis was the defining reason for admission, all main diagnoses were decodified and four primary outcomes were analyzed: total number of admissions in patients with GCA, admissions attributable to GCA (being GCA the main diagnosis), admissions with GCA-associated stroke and admissions attributable to GCA-associated stroke (being stroke the main diagnosis). GCA-associated stroke was defined by both the presence of stroke (codes I61, I62.9 and I63), AION (code H47.01) or TIA (code G45) in GCA patients.

These outcomes were compared between the years of the pandemic (2020 and 2021) and the most recent pre-pandemic period (2016–2019). Furthermore, to evaluate the incidence and distribution of GCA and GCA-associated stroke during the different stages of the pandemic, seven periods were considered: the first wave (March–April 2020), the post-lockdown period (June–July 2020), the second wave (October–November 2020), the third wave, coexisting with the first and second vaccine dosing in the elderly population (January–February 2021), the fourth wave (March–April 2021), the fifth wave (June–July 2021) and the third vaccination period in patients older than 70 years (October–November 2021). These intervals and dates were defined according to the COVID-19 epidemiology and the waves described in Spain, as well as according to the national vaccine policy implemented during 2020 and 2021 [31–33].

Finally, the ICD-10 coding was also used to analyze CRF. Patients were tagged as hypertensive if they had a diagnosis of primary hypertension (code I10), hypertensive cardiac disease (I11), hypertensive chronic kidney disease (I12), hypertensive cardiac and chronic kidney disease (I13) or secondary hypertension (I15). Diabetes included type 1 diabetes mellitus (E10), type 2 diabetes mellitus (E11) and other types of diabetes mellitus (E12). High cholesterol was defined by pure hypercholesterolemia (E78) or hyperlipidemia (E78.2 and E78.5) and obesity by the homonymous code E66. Smoking was classified according to tobacco consumption (Z72.0) or nicotine dependence (F17) and alcohol according to alcohol related disorders (F10).

2.3. Statistical analysis

Categorical variables were reported as frequencies and percentages while continuous variables were presented as mean and standard deviation. Bivariate comparisons of quantitative and qualitative variables were performed using the Kruskal-Wallis test, U Mann-Whitney test, and the Chi2 test. Incidence was expressed by 100,000 national admissions and rates or proportions of GCA and GCA-associated stroke as percentages of the overall admissions in patients with GCA.

First, we compared the annual incidence and the proportion of admissions with or because of GCA and GCA-associated stroke between the pre-pandemic years (2016–2019) and 2020 or 2021, respectively. Second, we analyzed the distribution of GCA and GCA-associated stroke admissions for each pandemic period, considering the subsequent waves and the third vaccination period in patients older than 70 years. Herein, and to determine the impact of COVID-19 disease and vaccine on the epidemiology of GCA, the different periods were compared with the same months in 2016–2019. Finally, we performed a binary logistic regression analysis to determine if each of these bi-monthly intervals were associated with a higher GCA-associated stroke risk. For adjustment, age, male sex, baseline CRF and COVID-19 diagnosis during admission were considered.

All statistical analyses were performed using IBM SPSS for Windows (IBM Corp, Armonk, NY). All tests were two-tailed and only p values <0.05 were considered as significant.

3. Results

3.1. Population characteristics

Between 2016 and 2021,17,268 hospital admissions in patients diagnosed with GCA were reported in the SNHDD registry. The population characteristics are shown in Table 1. The mean age was 80.9 years and 63.5% of the patients were female. Regarding classical CRF, 65.6% of the patients were identified as hypertensive, 31.4% as diabetic, 38.8% as hypercholesterolemic and 7.5% as obese. Smoking was reported in 4.3% and alcohol consumption in 2.7%. GCA was the cause of admission in 21.2% of the patients, and 8.6% were consistent with stroke (ischemic stroke 3.6%, TIA 1.7%, AION 2.8% and hemorrhagic stroke 0.5%). Stroke was the cause of admission in 4.8% of the cases overall. The mean average in-hospital stay was 9.3 days and the global mortality was 7% (1206 deaths).

3.2. Differences in the incidence of GCA and GCA-associated stroke during the pandemic

Table 2 illustrates epidemiological data of admissions related with GCA in Spain from 2016 to 2021. The incidence of admissions associated with GCA was higher in 2020 (79.3 per 100,000 national admissions) and in 2021 (80.8 per 100,000 national admissions) than in the pre-pandemic period (mean 72.4 per 100,000 national admissions, $p < 0.001$). By contrast, the admissions attributable to GCA itself were lower in 2020 than in the previous years (19.7% vs 21.7% of total admissions in GCA cases; $p = 0.003$).

Regarding ischemic events, both the proportion of admissions with GCA-associated stroke and the incidence of GCA-associated stroke were higher in 2020 (10.2% of all admissions in GCA patients and 8.1 per 100,000 national admissions, respectively) and in 2021 (9.5% of all admissions in GCA patients and 7.7 per 100,000 national admissions, respectively) than in the 2016–2019 period (7.9% of all admissions in GCA patients and 5.7 per 100,000 national admissions, respectively, $p = 0.05$). Likewise, the rate of admissions attributable to GCA-associated stroke was higher during 2020 (5.5% of all admissions in GCA patients and 4.4 per 100,000 national admissions, respectively) and during 2021 (5.6% and 4.5 per 100,000 national admissions in 2021, respectively) compared with the pre-pandemic period (4.5% of all admissions in GCA patients and 3.2 per 100,000 admissions in 2016–2019, respectively, $p = 0.01$).

Table 1
Population characteristics.

	Admissions in patients with Giant Cell Arteritis ($N = 17,268$)
Female N (%)	10,966 (63.5)
Age (years) (Mean, SD)	80.9 (8.7)
Cardiovascular risk factors	
Hypertension N (%)	11,318 (65.6)
Diabetes N (%)	5416 (31.4)
Cholesterol N (%)	6714 (38.8)
Obesity N (%)	1292 (7.5)
Smoking habit N (%)	734 (4.3)
Alcohol consumption N (%)	468 (2.7)
Diagnoses or events during admission	
GCA as admission cause	3659 (21.2)
GCA-associated stroke	1477 (8.6)
Ischemic stroke	619 (3.6)
TIA	288 (1.7)
AION	478 (2.8)
Hemorrhagic stroke	92 (0.5)
GCA-associated stroke as admission cause	829 (4.8)
Outcomes	
ICU admission N (%)	590 (3.4)
Mortality N (%)	1206 (7)
Admission- length stay (days) mean (SD)	9.3 (9.5)
ICU admission- length stay (days) mean (SD)	4.8 (7.9)

SD: Standard deviation, GCA: Giant cell arteritis, Cerebrovascular accident related to Giant cell arteritis, TIA: Transient ischemic attack, AION: Anterior ischemic optic neuropathy, ICU: Intensive Care Unit.

3.3. Differences in GCA and GCA-associated stroke incidence within pandemic periods

Since the epidemiology of GCA, including the rate of stroke, varied during 2020 and 2021, a bi-monthly-analysis of both GCA admissions and GCA-associated stroke incidence was performed to clarify the impact of the different COVID-19 waves and the potential influence of the SARS-CoV-2 vaccine (Table 3, Fig. 1).

Compared with the same months in 2016–2019, the incidence of admissions in GCA patients decreased during the first wave (62.3 vs 78.1 per 100,000 national admissions, $p < 0.001$). On the contrary, the incidence of admissions in patients with GCA was higher in the second wave (82.9 vs 70.5 per 100,000 national admissions, $p < 0.001$), in the fifth wave (85.2 vs 71.9 per 100,000 national admissions, $p < 0.001$) and in the period coinciding with the third vaccine dose in elderly patients (90.8 vs 70.5 per 100,000 national admissions, $p < 0.001$), (Table 3, Fig. 1.A).

In addition, several differences with the pre-pandemic period were found when the rates of admissions attributable to GCA and the proportions of admissions with or because of stroke were compared (Table 3, Fig. 1.B, 1. C and 1.D). The proportion of admissions with GCA-associated stroke in the post-lockdown period was higher than in previous years (12.6% vs 9.1% of all admissions in patients with GCA, $p = 0.023$). In the second wave, when a 16% of GCA patients were admitted with COVID-19, the proportion of admissions attributable to GCA was lower than other years (17.1% vs 22.1% of all admissions in GCA patients, $p = 0.017$). Likewise, during the third wave, when 18.2% of patients presented COVID-19, less patients were admitted because of GCA itself (14.9% vs 19.2% of all admissions in GCA patients, $p = 0.037$). On the other hand, both a higher rate of GCA-associated stroke (12% vs 6.7% of all admissions in GCA patients, $p < 0.001$) and more admissions attributable to GCA-associated stroke (6.7% vs 3.6% of all admissions in GCA patients, $p = 0.006$) were reported in this period compared with 2016–2019. Finally, it should be highlighted that a higher proportion of patients during October–November 2021 (third vaccine in patients older than 70 years) were admitted because of GCA-associated stroke (6.6% vs 4.1% of all admissions in patients with GCA, $p = 0.016$).

3.4. Impact of pandemic waves and vaccination periods on GCA-associated stroke

In order to determine whether the different periods related to COVID-19 waves and/or SARS-CoV-2 vaccines, entailed a higher risk of stroke in the setting of GCA, a binary logistic regression analysis considering age, sex, CRF and COVID-19 during admission, for each bi-monthly period, was performed (Fig. 2, Table 4). Only patients admitted during the third wave, concurring with the first and second vaccine in the elderly (OR = 1.89, 95% CI 1.22–2.93), and during the third vaccination period in patients older than 70 years (OR = 1.66, CI 1.11–2.49), presented a higher GCA-associated stroke risk compared with the same months in previous years. No similar increased risk was seen among patients admitted during other periods of the study.

Table 2
Epidemiology of GCA and GCA-associated stroke between 2016 and 2021 in Spain.

	2016 (*N* = 3,895,317)	2017 (*N* = 3,972,586)	2018 (*N* = 4,026,251)	2019 (N = 3,971,324)	2020 (N = 3,516,107)	2021 (N = 3,706,163)
Admissions in patients with GCA						
N	2757	2844	2822	3052	2788	2.995
Incidence per 100,000 admissions	70.1	71.6	70.1	76.9	**79.3**	**80.8**
Admissions attributable to GCA						
N (%)	621 (22.5)	605 (21.3)	598 (21.2)	659 (21.6)	**548 (19.7)**	628 (21)
Incidence per 100,000 admissions	15.9	15.2	14.9	16.6	15.6	16.9
Admissions with GCA-associated stroke						
N (%)	214 (7.8)	219 (7.7)	242 (8.6)	233 (7.6)	**285 (10.2)**	**284 (9.5)**
Incidence per 100,000 admissions	5.5	5.5	6	5.9	**8.1**	**7.7**
Admissions attributable to GCA-associated stroke						
N (%)	120 (4.4)	138 (4.9)	123 (4.4)	127 (4.2)	**153 (5.5)**	**168 (5.6)**
Incidence per 100,000 admissions	3.1	3.5	3.1	3.2	**4.4**	**4.5**

GCA: Giant cell arteritis. Percentages are related to the number of admissions in patients with GCA, while the incidence is expressed in number of admissions per 100,000 national admissions. Statistically significant differences when compared to the incidence of previous years ($p < 0.05$) are highlighted in bold.

Table 3
GCA and GCA-associated stroke epidemiology during the COVID-19 pandemic periods in Spain.

	First wave (March–April 2020)	Post-lockdown period (June–July 2020)	Second wave (October–November 2020)	Third wave (January–February 2021)	Fourth wave (March–April 2021)	Fifth wave (June–July 2021)	Third vaccine (October–November 2021)
Admissions in patients with GCA (Incidence per 100,000 admissions)	**369 (62.3)**	507 (86.5)	**486 (82.9)**	451 (73)	502 (81.3)	**526 (85.2)**	**561 (90.8)**
Admissions with COVID-19 N (%)	–	4 (0.8)	78 (16)	82 (18.2)	20 (4)	12 (2.3)	13 (2.3)
Admissions attributable to GCA N (%)	66 (17.9)	124 (24.5)	**83 (17.1)**	**67 (14.9)**	109 (21.7)	132 (25.1)	116 (20.7)
Admissions with GCA-associated stroke N (%)	28 (7.6)	**64 (12.6)**	47 (9.7)	**54 (12)**	41 (8.2)	52 (9.9)	53 (9.4)
Admissions attributable to GCA-associated stroke N (%)	16 (4.3)	35 (6.9)	19 (3.9)	**30 (6.7)**	25 (5)	31 (5.9)	**37 (6.6)**

GCA: Giant cell arteritis. Percentages are related to the number of admissions in patients with GCA, while the incidence is expressed in number of admissions per 100,000 national admissions. Statistically significant differences when compared to the incidence of previous years ($p < 0.05$) are highlighted in bold.

4. Discussion

This nation-wide epidemiological study explores the incidence of GCA and the risk of GCA-associated stroke during the COVID-19 pandemic. Our results suggest that COVID-19 disease and, especially, SARS-CoV-2 vaccine, might be responsible for the higher rate of GCA-associated stroke reported in this period, leading to the increased incidence of admissions among patients with GCA during 2020 and 2021.

Previous works have already identified that COVID-19 disease and immunization, especially with mRNA-vaccines, can trigger the onset of GCA and GCA flares [16,17,19,24,25,27,28]. An analysis based on the WHO safety report database by Mettler et al. found that COVID-19 vaccines might be actually associated with an increased number of diagnosis of GCA, identifying a potential safety signal and raising concerns about repeated vaccinations [24]. In addition, some authors have proposed that after SARS-CoV-2 vaccination, GCA can present with atypical features, including a higher rate of neuro-ophthalmological and vascular complications [19,20,25,26,28]. However, all these assumptions should be interpreted cautiously, since these data are mostly based on case reports, small series or single-center studies. Moreover, other authors have not confirmed a significantly higher incidence of GCA during the COVID-19 pandemic [18,29,30]. For example, Kaulen et al. only found one case of GCA in >200,000 inhabitants who received SARS-CoV-2 vaccinations in Germany [22]. On the other hand, it has been shown that general health care and, particularly, the diagnosis and outpatient management of autoimmune diseases, including GCA, has been greatly influenced by the pandemic [30,34]. Accordingly, the incidence, clinical onset and severity of the disease may have changed during this period not only by COVID-19 itself, but also influenced by a more difficult access to health facilities for clinical conditions other than COVID-19. Altogether, we believe that this large study can help clarify the epidemiology of GCA and the impact of COVID-19 waves and vaccines during the first two years of the pandemic.

Overall, our results show that the incidence of GCA rose during 2020

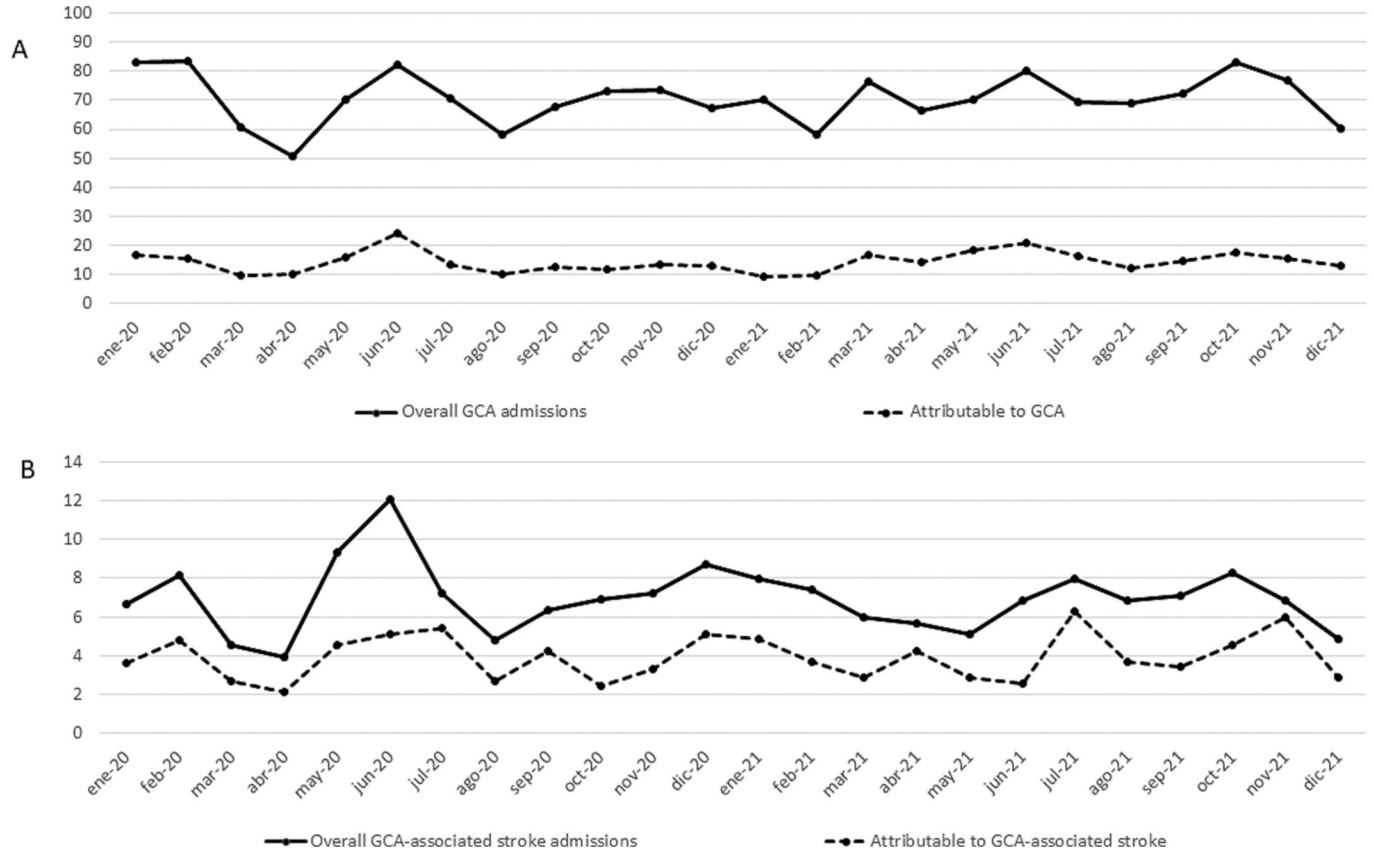

Fig. 1. Incidence of GCA and GCA-associated stroke in Spain during the COVID-19 pandemic in Spain.
Footnote: The figure represents the monthly incidence of GCA (A) and GCA-associated stroke (B) admissions during the COVID-19 pandemic in Spain. Incidence is expressed by 100,000 annual national admissions.

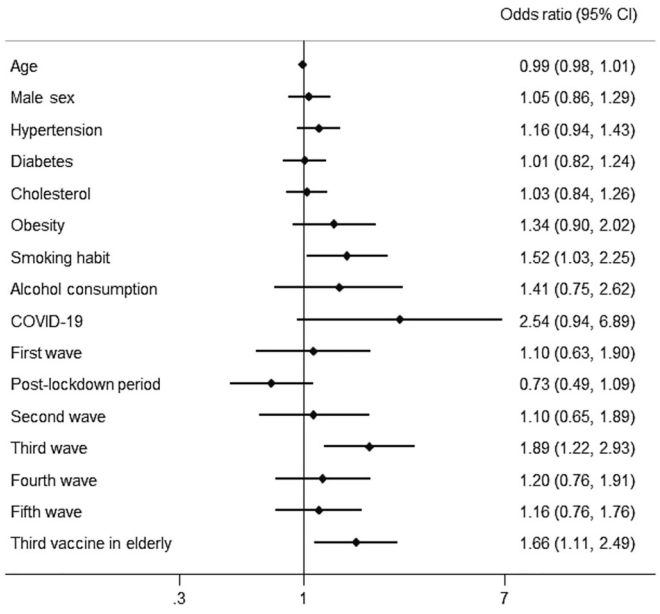

Fig. 2. Factors related to GCA-associated stroke during the COVID-19 pandemic in Spain.
Footnote: The figure represents the binary logistic regression analysis to determine factors related to GCA-associated stroke risk during the pandemic, including the seven periods of the COVID-19 pandemic. For adjustment, age, male sex, baseline CRF and COVID-19 diagnosis during admission were considered.

Table 4
Adjusted risk of GCA-associated stroke per study periods.

	OR	95% CI
First wave	1.10	0.63–1.90
Post-lockdown period	0.73	0.49–1.09
Second wave	1.10	0.65–1.89
Third wave	**1.89**	**1.22–2.93**
Fourth wave	1.20	0.76–1.91
Fifth wave	1.16	0.76–1.76
Third vaccine in elderly	**1.66**	**1.11–2.49**

Each period was adjusted by age, male sex, hypertension, diabetes, hypercholesterolemia, obesity, smoking, alcohol consumption and COVID 19.

and 2021, as previously noticed [16,24,27,28]. These figures seem to be mostly determined by admissions associated with COVID-19 and by the higher incidence and proportion of admissions with or because ischemic events, supporting the hypothesized effect of both, the virus and the vaccine, on vascular events in GCA patients (19,25,26,28). Besides, this effect has not been uniform in our population during the different periods of the pandemic. In the first place, the dramatic reduction of GCA admissions during March and April 2020, when COVID-19 was not yet included in the ICD-10 coding, was followed by an increase of cerebrovascular events in the post-lockdown period. Therefore, the diagnostic and therapeutic delay during the first wave, with a collapsed emergency system nationwide, probably led to a higher rate of subsequent complications, as other authors have already described [30,34]. On the other hand, the higher incidence of GCA admissions identified in our study during the second COVID-19 outbreak following summer 2020 was mostly related to COVID-19, and not to GCA or GCA-CVA themselves.

In Spain, the national SARS-CoV-2 vaccination campaign began at the end of December of 2020 [31]. The vaccine policies were initially focused on the elderly and on those living in nursery homes, who were particularly vulnerable to COVID-19 during the first two waves [10,32,33]. Accordingly, the protective effect was not evident until the fourth and fifth waves, as seen in our population and as reported by Barandalla et al [31]. However, a significant increase in ischemic events was identified in January–February 2021 and October–November 2021, in close temporal coincidence with the first two doses of the vaccine in patients older than 80 and the third dose in patients older than 70, respectively. Therefore, the rising rates of GCA-associated stroke identified in patients with GCA during these periods, as confirmed in the multivariate analysis, supports the role of mRNA-vaccine on the subsequent risk of ischemic phenomena in GCA [5,17,19,35].

Despite the many uncertainties in the pathophysiology of GCA, the association of the disease with certain infectious agents has been previously reported [5–8]. Analogous to other autoimmune or rheumatic diseases, the current pathogenic model accepts that GCA develops in genetically predisposed individuals exposed to a number of triggers, including infections. This hypothesis is well-accepted in other conditions such as CAPS or polyarteritis nodosa, where infections have shown to be strongly associated with the disease onset [6,36]. Both bacteria and virus has been implicated. *Escherichia coli*, *Propionibacterium acnes*, *Coxiella burnetti*, *Parvovirus B19*, *Cytomegalovirus* and *Varicella zoster*, have all been associated with GCA or granulomatous angiitis of the CNS [5–8]. The association between SARS-CoV-2 infection and/or COVID-19 vaccines and GCA or subsequent CVA, as seen in our population, seems also plausible given the proinflammatory and prothrombotic character of both the infection and the vaccine [16,17,19,37].

We should acknowledge several limitations of the present study. Due to the database structure, essential information such as antiplatelet, anticoagulant, tocilizumab or glucocorticoid treatment before and during admission, and more detailed data about the diagnosis and clinical course of GCA, including the extent of the disease and the number or type of vessels involved, was lacking. Secondly, we were not able to retrieve information about COVID-19 infection prior to vaccination, immunological status and, importantly, about the specific vaccine given. However, despite these limitations, we believe that the size of the study population, the nationwide spectrum of the study and the statistical power of the analysis make our data clinically relevant. Moreover, the proportion of individuals effectively vaccinated within the analyzed periods, particularly within older people, was very high in Spain, most of them receiving mRNA-based vaccines [31,38]. Therefore, the assumption that most of the population of the study received such vaccines during the presumed periods of vaccination analyzed is likely to be correct. Thirdly, given the need to fit yearly time periods, the first two months of 2020 preceded the major COVID-19 outbreak in Spain. Therefore, counting these two months within the pandemic period should have provided an underestimation of the proportion of cases of GCA and GCA-associated stroke collected in this timeframe. Trends in Fig. 2 support this observation. Another caveat is the complex interaction over two years between older age, COVID-19 severity, COVID-19 vaccination, COVID-19 mortality, and GCA higher incidence. In Spain, 98,900 deaths due to COVID-19 were reported during 2020 and 2021. However, estimates derived from the excess mortality data during the same period are of 162,000 (1.64-fold greater) [39]. This huge and disproportionate high mortality mostly occurred among the elderly, the population at higher risk for of developing GCA.

In conclusion, this nationwide epidemiological study confirms a higher risk of CVA in patients with GCA during the pandemic, probably related, at least in part, to mRNA-SARS-CoV-2 vaccines. Therefore, our findings rise concerns about the potential risk of vascular complications after SARS-CoV-2 vaccination in patients with GCA, as already suggested [16,18]. Whilst the initial indication and benefit of SARS-CoV-2 immunization in this population was obvious, given the favorable effect in terms of COVID-19 severity among elderly patients, the need for repeated doses does not seem that clear [10,31,33]. A third dose of the vaccine has been advocated to confer adequate immunization in GCA patients, many of them under methotrexate and glucocorticoid treatment which may results in lower neutralizing activity and cellular immune protection than healthy controls [40]. However, the inclusion of GCA among the potential conditions associated with the Autoimmune/inflammatory syndrome induced by adjuvants (ASIA), and, particularly, with post-COVID-19 vaccination ASIA [41,42], should be also taken into account. Moreover, according to our results, the future vaccine policies must weigh the risk of severe COVID-19 against the risk of flare and, especially, of stroke in patients with GCA. Therefore, knowing the actual immunological status of the patients -probably including cellular immunity in the equation in patients with insufficient humoral response-, their baseline cardiovascular risk and also the virulence of the predominant variant of the coronavirus would help individualize the indication of future subsequent doses.

Funding

Víctor Moreno-Torres received a grant from the Academia Medico-Quirúrgica Española. Guillermo Ruiz-Irastorza was supported by the Department of Education of the Basque Government, research grant IT 1512–22.

Submission declaration and authorship

The present work has not been published previously, it is not under consideration for publication elsewhere and, if accepted, will not be published elsewhere. The work has been approved by all author, who have made substantial contribution to the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Victor Moreno-Torres reports financial support was provided by Academia Médico-Quirúrgica Española. Guillermo Ruiz-Irastorza reports financial support was provided by Department of Education of the Basque Government.

Data availability

Data will be made available on request.

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