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Research Article

Prevalence and Impact of Cerebrovascular Risk Factors in Patients with Giant Cell Arteritis: An Observational Study from the Spanish National Registry

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Abstract

Objectives: To assess the prevalence and impact of cerebrovascular risk factors (CRF) on major cerebrovascular events in patients with Giant Cell Arteritis (GCA).

Methods: Analysis of the patients diagnosed with GCA identified in the Spanish Hospital Discharge Database between 2016 and 2018. Admissions due to cerebrovascular events (CVE, composed by stroke and transient ischemic attack) were compared to the admissions due to other causes. The factors related to cerebrovascular events were assessed by a multivariate logistic regression analysis.

Results: 8,474 hospital admissions from patients diagnosed with GCA were identified. Mean age was 80.8 years and 36.4% were male. 67.2% were hypertense, 27.8% diabetic, 36.7% dyslipidemic, 14.2% smokers and 6.8% presented prior atherosclerosis diagnosis. Overall mortality rate was 6.5%. 3.4% of the admissions were motivated by CVE (stroke in 2.8% and TIA in 0.6%). When compared with admissions due to other causes, the patients who suffered

from CVE presented a higher rate of male sex (36.2 vs 43.5 %, p=0.007), hypertension (66.9% vs 74.4%, p=0.004), diabetes (27.6% vs 33.7%, p=0.016) and atherosclerosis (6.6% vs 10.2%, p=0.0017). After adjustment, male sex (OR= 1.35, 95% CI 1.06-1.72) and mainly hypertension (OR=1.44, 95% CI 1.11-1.90) were associated with a higher risk of CVE.

Conclusion: Hypertension, along with male sex, was the strongest risk factor for cerebrovascular events in GCA patients. In these high-risk patients, antiplatelet therapy should be re-considered and evaluated in prospective studies.

Keywords: Cerebrovascular events; Cardiovascular risk factors; Giant cell arteritis

Abbreviations: CI: Confidence interval; CRF: Cardiovascular risk factors; CVE: Cerebrovascular event; GCA: Giant cell arteritis; ICD: International Classification of Diseases; ICU: Intensive care Unit; SNHDD: Spanish Hospital Discharge Database; TIA: transient ischemic attack

1. Introduction

Giant Cell Arteritis (GCA) is a chronic granulomatous vasculitis affecting the aorta and its main ramifications, with special predilection for the extracranial branches of the carotid artery [1]. GCA is a rare disease that presents almost exclusively in patients over 50 years-old. The highest prevalence has been described in Northern Europe countries, where females are also more frequently affected with a ratio that reaches 3 to 1 [2]. Clinically, the disease usually presents an insidious course with general manifestations including fever, asthenia or weight-loss, along with local symptoms due to arterial inflammation and vascular deficit such as headache, jaw claudication or transient vision loss [3]. These vascular events may indeed occur in up to 20-50% of patients with GCA and are responsible of the sometimes-abrupt onset of the disease. Apart from the extra-cranial branches of the carotid artery that determine the classic symptoms of the disease, cerebral ischemic events can also be seen, being the vertebrobasilar territory the most commonly affected [4,5]. Finally, severe arterial compromise can even lead to established ischemic events in theses territories, one of the most severe complications of the disease, with a high morbidity and mortality impact [6, 7]. Usually, these ischemic events in GCA tend to occur during the inflammatory period of the vasculitis [8]. Also, several studies have reported a higher risk of cerebrovascular events in the presence of classical cardiovascular risk factors [7,9-12]. In light of the previous, prophylactic antiplatelet therapy was initially encouraged in the original EULAR recommendations [13]. However, since other reports did not confirm a solid effect of aspirin in GCA, aspirin use was no longer routinely recommended in the latest recommendations [14]. Therefore, the aim of our study was to analyze the prevalence and impact of Cerebrovascular Risk Factors (CRF) in patients with GCA, to identify those who are at higher risk and could potentially benefit from antiplatelet therapy.

2. Materials and Methods

2.1. Patients

We performed an observational and retrospective analysis with data from The Spanish Hospital Discharge Database (SNHDD), a registry that belongs to the Spanish Ministry of Health. SNHDD includes demographic and epidemiological data and up to 20 discharge diagnoses carried out during admission defined by the International

Classification of Diseases (ICD-10) from 1 January 2016. We selected hospital admissions from 1 January 2016 to 31 December 2018 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 diagnostic list. The study complies with the Declaration of Helsinki and was approved by the local research ethics committee.

2.2. Assessment of cerebrovascular events and identification of cardiovascular risk factors

Once patients with CGA diagnosis were selected, those whose admission was attributable to cerebrovascular events (CVE) were identified. CVE were considered if the main diagnosis was acute ischemic stroke (code I63) or transient ischemic attack (TIA, code G45). In order to analyze the CRF, patients were tagged to suffer from any of them if the proper ICD-10 code or any other disease whose definition implied the mentioned risk factors was identified in the coding list. To this purpose, patients were identified as hypertense if they presented 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 was identified by type 1 diabetes mellitus (E10), type 2 diabetes mellitus (E11) and other types of diabetes mellitus (E12). Dyslipidemia was defined by hypercholesterolemia (E78) and hyperlipidemia (E78.2 and E78.5). Tobacco was classified according to tobacco consumption (Z72.0) or nicotine dependence (F17). Atherosclerosis was considered by the homonymous code I70.

2.3. Statistical analysis

Categorical variables were reported as frequencies and percentages and continuous variables were presented as mean and standard deviation. The significance of baseline differences between admissions attributable to CVE and those who did not was determined by the chi-square, Fisher's or Student's t test as appropriate. A multivariate logistic regression analysis was performed to determine the factors related to CVE in patients with GCA. For all the analyses, a significance level of 0.05 was set. Statistical analysis was performed using SPSS version 26.0 (IBM, Spain).

3. Results

3.1. Patient's characteristics

8,474 admissions in GCA diagnosed patients were identified between 2016 and 2018. The characteristics of the admissions and population are shown in Table 1. Overall, the mean age was 80.8 years-old and 36.4% were male. Regarding CRF, 67.2% were hypertense, 27.8% suffered from diabetes, 36.7% from dyslipidemia and in 14.2% smoking habit was identified. 6.8% presented prior atherosclerosis diagnosis. Overall mortality rate was 6.5% and the mean average stay was 9.3 days.

3.2. Cerebrovascular events

Overall, 3.4% of admissions were attributable to a cerebrovascular event (ischemic stroke in 2.8% and TIA in 0.6%). When compared to admissions due to other causes (Table 2), the patients who suffered from CVE presented a higher rate of male sex (36.2 vs 43.5 %, p=0.007), a higher burden of cardiovascular risk factors such as hypertension (66.9% vs 74.4%, p=0.004) or diabetes (27.6% vs 33.7%, p=0.016) and more atherosclerosis (6.6% vs 10.2%, p=0.0.02). No differences were found regarding age, ICU admission, mortality or average stays. Finally, a multivariate analysis was performed to identify factors related to cerebrovascular events (Table 3). After adjustment,

male sex (OR= 1.35, 95% CI 1.06-1.72) and hypertension (OR=1.44, 95% CI 1.11-1.90) were associated with a higher risk while diabetes (OR=1.24, 95% CI 0.96-1.60) and atherosclerosis (OR=1.44, 95% CI 0.96-2.14) did not.

Admissions (N)	8,474
Age (years) (Mean, SD)	80.8 (8.7)
Male sex (N, %)	5386 (36.4%)
Hypertension (N,%)	5691 (67.2%)
Diabetes (N,%)	2358 (27.8%)
Dyslipidemia (N, %)	3111 (36.7%)
Smoking (N,%)	1205 (14.2%)
Atherosclerosis (N,%)	573 (6.8%)
ICU admission (N,%)	273 (2.2%)
Death (N,%)	549 (6.5%)
Stay (days) (Mean, SD)	9.3 (9.3)

GCA: Giant cell arteritis, SD: Standard deviation, ICU: Intensive care Unit
Quantitative data are expressed in mean and standard deviation (SD), qualitative data as number and percentage (%)

Table 1: Admitted patients in Spain with GCA.

	Cerebrovascular events (N=285)	**Other admission causes (N=8,189)**	**p-value**
Age (Mean, SD)	80.3 (8.7)	80.8 (8.7)	0.356
Male (N,%)	124 (43.5%)	2964 (36.2%)	0.007
Hypertension (N,%)	212 (74.4%)	5479 (66.9%)	0.004
Diabetes (N,%)	96 (33.7%)	2262 (27.6%)	0.016
Dyslipidemia (N, %)	115 (40.4%)	2996 (36.6%)	0.109
Aterosclerosis (N,%)	29 (10.2%)	544 (6.6%)	0.017
Smoking (N,%)	38 (13.3%)	1167 (14.3%)	0.37
ICU admission (N,%)	10 (3.5%)	263 (3.2%)	0.437
Mortality (N,%)	22 (7.7%)	527 (6.4%)	0.224
Average stay (days) (Mean, SD)	10 (10.6)	9.3 (9.3)	0.196

SD: Standard deviation, ICU: Intensive care Unit.
Quantitative data are expressed in mean and standard deviation (SD), qualitative data as number and percentage (%)

Table 2: Differences among admissions related to a cerebrovascular event.

	OR	95% CI
Age	0.99	0.98-1.01
Male sex	1.35	1.06-1.72
Hypertension	1.44	1.11-1.90
Diabetes	1.24	0.96-1.60
Atherosclerosis	1.44	0.96-2.14

OR: Odds ratio, CI: Confidence interval.

Table 3: Factors related to cerebrovascular event in patients with giant cell arteritis.

4. Discussion

This nation-wide analysis is one of the largest studies exploring factors related to cerebrovascular events in GCA, confirming that male sex and hypertension determine a higher risk of stroke in patients with this disease. In our registry, 3.4% of GCA patients were admitted because of either stroke or TIA. While ischemic complications have been described in up to 50% of patients, severe events such as TIA and stablished stroke have been identified in a similar proportion to ours [5,10,15]. Therefore, these data highlight the remarkable CVE risk in GCA, a similar proportion to ours GCA, lower than Takayasu´s arteritis but significantly higher than in other systemic vasculitides such as ANCA-associated vasculitis [16-18]. Despite the relative low prevalence, their impact is obviously significant. In GCA, ischemic events occur in relation to intimal hyperplasia that eventually occludes the lumen of the vessel [19]. However, it has been pointed out that cardiovascular risk factors may increase the risk of ischemic events in these patients, since they are likely to be involved in the development of thrombotic phenomena on the damaged vessel, as occurs in atheromatous arterial disease [10,12,20,21]. In our study, patients with CVE presented a higher rate of male sex, hypertension, diabetes and more atherosclerosis, confirming that CRF contribute to the inflammatory injury of the vessel. However, in the multivariate analysis, only male sex and hypertension were related to CVE. Similar findings have been described by others, confirming that hypertension is the main factor related to cerebral ischemic events in the setting of GCA, over diabetes, dyslipidemia or tobacco [5,7,10]. Besides, hypertension is also the stronger risk factor of stroke in the general population and male sex presents an inherent higher risk of stroke [22].

In the light of the aforementioned, diagnosis and treatment of atherosclerotic disease might play a major role during GCA management. In addition to prompt identification and treatment of the cardiovascular risk factors, questions about prophylactic use of antiaggregant therapy arise. Prior retrospective cohorts have shown that aspirin-treated groups developed less cerebrovascular complications [20,21], while more recent studies, including one metanalysis, have not confirmed that antiplatelet or anticoagulant therapy could reduce severe ischemic events in GCA [8,23,24]. After these, the latest EULAR recommendations did not encourage again prophylactic antiplatelet treatment as in the original guideline. However, the not despicable prevalence of serious CVE and the prevalence and impact of the cerebrovascular risk factors in our cohort suggest that probably antiaggregant use in GCA should be more carefully analyzed. To this purpose, other studies should also consider the cardiovascular risk factors, atherosclerosis prevalence as well as the bleeding risk, in order to individualize the best approach. Our study presents several

limitations. Due to the database configuration, essential information such as antiplatelet, anticoagulant, tocilizumab or steroid treatment prior to the admission, and more complete data about the course and diagnosis of the disease, including the number of confirmatory biopsies, the extent of disease, the number or type of vessels involved, and length of disease, among others, was lacking. This information could have yielded a more complete understanding of the factors related to cerebrovascular events. In addition, cerebrovascular events were compared with admissions due to other causes and not to health-control patients. On one hand, this could have diminished the power of our findings. On the other hand, the weight of the risk factors was evaluated with other diseases and is not as accurate as when compared to controls. Altogether, we were aware of the limitations of the database through the study design and we only analyzed reliable and categorical data such as CVE. Despite these pitfalls, we believe that our results are valid and robust although prospective and multicentric studies are needed to confirm our findings. In conclusion, our study reveals that hypertension, along with male sex, was the strongest risk factor of cerebrovascular events in GCA patients. In these high-risk patients, the debate about antiplatelet therapy should be re-considered and evaluated in prospective studies.

Statements and Declarations

Conflicts of interest

None

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Ethics approval

The study was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro in accordance with the Declaration of Helsinki.

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