The Association Between Giant Cell Arteritis and Ischemic Heart Disease: A Population-Based Cross-Sectional Study

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ABSTRACT: **Background:** Patients with giant cell arteritis (GCA) suffer from inflammatory diseases often treated by large amounts of corticosteroids. Whether this inflammatory burden also carries an increased risk for cardiovascular morbidity, and especially ischemic heart disease, is not clearly established.

Objectives: To clarify the linkage between GCA and ischemic heart disease.

Methods: In a cross-sectional study, we assessed the association between GCA and ischemic heart disease, adjusting for cardiovascular risk factors, among GCA patients and matched controls using the database of the largest healthcare provider in Israel.

Results: The study group was comprised of 5659 GCA patients and 28,261 age and gender matched controls. The proportion of ischemic heart disease was higher in the GCA group (27.5% vs. 12.5% among controls, odds ratio 2.65). Diabetes mellitus, hypertension, hyperlipidemia and smoking were also found to have higher concurrency in GCA. After stratifying for those cardiovascular co-morbidities using logistic regression, GCA remained independently associated with ischemic heart disease with an odds ratio of 1.247 (1.146–1.357 $P < 0.001$).

Conclusions: GCA is associated with both cardiovascular risk factors and ischemic heart disease. Healthcare professionals should not overlook this aspect of the disease when managing GCA patients.

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Giant cell arteritis (GCA) is the most common primary systemic vasculitis involving predominantly the elastic, tissue-rich, large arteries of the aorta and its major branches located in the head and neck [1,2]. The inflammatory process leads to vessel scarring and narrowing and eventually to occlusion or severe stenosis, which can eventually lead to visual complications, cerebrovascular complications or aortic aneurysm formation [2].

An increased inflammatory burden and a propensity toward a hypercoagulable state have been hypothesized as the reason for an increased incidence of vascular events in patients with other autoimmune inflammatory conditions. It is well reported that other chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriatic arthritis, carry a similar increased risk for cardiovascular diseases [3-8].

In recent years several studies noted contradicting results regarding the risk of cardiovascular diseases in GCA patients [9-13]. This might suggest geoepidemiological variations affecting the overall risk due to varying degrees of sun exposure and endogenous vitamin D formation as well as a dissimilar impact of traditional risk factors of cardiovascular diseases among different populations [14].

Our study objective was to clarify the linkage between GCA and ischemic heart disease (IHD) using the medical database of the Clalit Health Services (CHS), the largest health maintenance organization in Israel. This database provided a high quality sample size and allowed us to stratify the association between GCA and IHD, while adjusting for traditional risk factors associated with cardiovascular diseases as well as different demographic characteristics.

PATIENTS AND METHODS

The study was designed as a cross-sectional study utilizing the CHS clinical database. CHS serves a population of approximately 4.4 million insured members from heterogeneous ethnic groups in Israel. CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative operating systems. Patients were defined as having GCA or IHD when recorded as having this condition on a discharge letter from the hospital

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or when registered as having this condition by a community physician. CHS performs the process of diagnosis validation by logistic checks (such as matching the diagnoses from different sources). The validity of the diagnoses in the CHS registry was demonstrated to be highly accurate [5;8;15-19]. Controls were randomly selected from the CHS clinical database in a ratio of five controls for each patient with the diagnosis of GCA. These controls were frequency-matched to cases regarding gender and age. Data available from the CHS database included age, gender, body mass index (BMI) and socioeconomic status (SES), and cardiovascular risk factors such as diabetes mellitus (DM), history of smoking, hypertension and hyperlipidemia. This study was approved by the ethics committee of CHS at the Soroka Medical Center, Beer Sheva, Israel.

SES was defined according to the poverty index of the member's residence as defined during the 2008 national census. The poverty index is based on several parameters, including household income, education, crowding, material conditions, and car ownership. It ranges from 1 to 20, based on cluster analysis, with 1 being the lowest SES and 20 the highest. In our study these layers were divided into tertiles (low, medium, and high).

The distribution of sociodemographic and clinical factors was compared for patients with and without GCA using a chi-square test for gender, SES and chronic disease diagnosis. A *t*-test was used for age and BMI. Interaction between IHD and GCA was studied among categorical variables and strata of continuous variables. A logistic regression model was used to estimate the association between GCA and the different factors, including IHD, in a multivariate analysis. Area under the curve was calculated for logistic regression models. Statistical crude odds ratio (OR) as well as 95% confidence interval (CI) are presented. Analysis was performed using R version 3.3.2 (R Core Team, Vienna, Austria).

Table 1. GCA patients and matched controls: basic characteristics

	No GCA N=28261	GCA N=5659	OR (95%CI)	*P* ratio
Age, years	67.8 ± 15.1	71.1 ± 15.6	1.02 (1.01–1.02)	‹ 0.001
Gender: female	19737 (69.8%)	3951 (69.8%)	1.00 (0.94–1.06)	0.975
BMI	28.2 ± 5.91	28.1 ± 5.60	1.00 (0.99–1.00)	0.084
SES: Low*	5437 (36.8%)	1966 (34.9%)	Ref.	Ref.
SES: Medium*	6236 (42.2%)	2339 (41.5%)	1.04 (0.97–1.11)	0.306
SES: High*	3092 (20.9%)	1336 (23.7%)	1.19 (1.10–1.30)	‹ 0.001
Hypertension	8413 (29.8%)	3586 (63.4%)	4.08 (3.84–4.33)	0.000
Hyperlipidemia	9841 (34.8%)	4372 (77.3%)	6.36 (5.95–6.80)	0.000
Diabetes	4638 (16.4%)	1824 (32.2%)	2.42 (2.27–2.58)	0.000
Smoking	4128 (14.6%)	1887 (33.3%)	2.92 (2.74–3.12)	0.000
IHD	3544 (12.5%)	1559 (27.5%)	2.65 (2.48–2.84)	0.000

SES = socioeconomic status, IHD = ischemic heart disease, GCA = giant cell arteritis, OR = odds ratio, CI = confidence interval

*As defined by the 2008 national census

Table 2. Interaction table of GCA and IHD patients by strata*

	Total N=33,920 (%)	No GCA N=28,261 (%)	GCA N=5659 (%)	OR (95%CI)	*P*
IHD	5103 (15.0)	3544 (12.5)	1559 (27.5)	2.65 (2.48–2.84)	0.000
Gender: female	3179 (13.4)	2226 (11.3)	953 (24.1)	2.50 (2.30–2.72)	0.000
Gender: male	1924 (18.8)	1318 (15.5)	606 (35.5)	3.01 (2.68–3.37)	0.000
Age: 18–44	10 (0.32)	4 (0.15)	6 (1.34)	8.81 (2.43–36.0)	0.001
Age: 45–69	912 (7.27)	615 (5.70)	297 (17.0)	3.39 (2.92–3.93)	0.000
Age: 70+	4181 (22.8)	2925 (19.7)	1256 (36.2)	2.31 (2.14–2.51)	0.000
SES: Low**	1713 (23.1)	1181 (21.7)	532 (27.1)	1.34 (1.19–1.50)	‹ 0.001
SES: Medium**	2082 (24.3)	1429 (22.9)	653 (27.9)	1.30 (1.17–1.45)	‹ 0.001
SES: High**	1042 (23.5)	675 (21.8)	367 (27.5)	1.36 (1.17–1.57)	‹ 0.001
BMI ≤ 25	1017 (19.7)	589 (17.2)	428 (24.5)	1.56 (1.36–1.80)	‹ 0.001
BMI › 25	2838 (24.7)	1717 (22.5)	1121 (29.0)	1.41 (1.29–1.54)	‹ 0.001
Hypertension	4381 (36.5)	3005 (35.7)	1376 (38.4)	1.12 (1.03–1.21)	0.006
Hyperlipidemia	4496 (31.6)	3022 (30.7)	1474 (33.7)	1.15 (1.06–1.24)	‹ 0.001
Diabetes	2538 (39.3)	1800 (38.8)	738 (40.5)	1.07 (0.96–1.20)	0.222
Smoking	1772 (29.5)	1181 (28.6)	591 (31.3)	1.14 (1.01–1.28)	0.033

IHD = ischemic heart disease, SES = socioeconomic status, BMI = body mass index (kg/m^2), GCA = giant cell arteritis, OR = odds ratio, CI = confidence interval

*Reference category for each stratum contains subjects without IHD

**As defined by the 2008 national census

RESULTS

The study was comprised of 5659 patients with GCA and 28,261 age and gender matched controls. The characteristics of the study population are presented in Table 1. The proportion of IHD in patients with GCA was increased compared with the prevalence in controls, 27.5% and 12.5%, respectively (OR 2.65, 95%CI 2.48–2.84, $P < 0.001$). In addition, the proportion of cardiovascular risk factors, namely hypertension, hyperlipidemia, DM, and history of smoking, were increased in patients with GCA. Table 2 shows the interaction between GCA and IHD. ORs for IHD in patients with GCA stratified by gender, age, SES, BMI, and cardiovascular risk factors are presented. Increased OR for IHD among patients with GCA was maintained in both females and males, in all age groups, for all BMI ranges, and across all SES strata. As seen in Table 3, GCA was identified as independently associated with IHD in a multivariate analysis (OR 1.247, 95%CI 1.146–1.357, $P < 0.001$). Age, male gender, history of smoking, DM, high BMI, hypertension and hyperlipidemia were also independently associated with IHD [Table 3].

DISCUSSION

In this large cross-sectional population-based study we found that GCA is independently associated with IHD even after adjusting for other known risk factors associated with

Table 3. Logistic regression – Covariates associated with IHD

	OR	95%CI	*P*
Age, per year	1.058	1.053–1.063	‹ 0.001
Gender (male vs. female)	2.546	2.316–2.799	‹ 0.001
BMI, 1 kg/m2 increment	1.011	1.003–1.018	0.005
SES: medium vs. low*	0.891	0.812–0.979	0.016
SES: high vs. low*	0.865	0.774–0.967	0.011
Hypertension	3.025	2.700–3.394	‹ 0.001
Hyperlipidemia	3.830	3.291–4.478	‹ 0.001
Diabetes	1.665	1.530–1.812	‹ 0.001
Smoking	1.493	1.363–1.635	‹ 0.001
GCA	1.247	1.146–1.357	‹ 0.001

BMI = body mass index (kg/m2), SES = socioeconomic status, IHD = ischemic heart disease, GCA = giant cell arteritis, OR = odds ratio, CI = confidence interval

*As defined by the 2008 national census

cardiovascular disease. Indeed, in recent years mounting evidence underlines the role inflammatory conditions have in the excessive risk of vascular events. Potential mechanisms include oxidative stress, endothelial dysfunction, harmful effect of inflammatory cytokines and pro-atherogenic effect of glucocorticosteroids [3,5,7-9].

Previous studies have indicated that a connection between IHD and GCA is inconclusive. Several reports found an increased risk for cardiovascular diseases among GCA patients. For example, a study by Tomasson et al. [20] found a hazard ratio (HR) of 1.7 for myocardial infarction in a case-matched study of GCA patients using the Health Improvement Network cohort from the UK. Ray and colleagues [12] observed an increased HR of 1.6 for cardiovascular disease in Ontario, Canada. Both studies did not stratify for traditional risk factors associated with cardiovascular diseases. Amiri and co-authors [9] reported an increased HR of 1.7 in a population study in British Colombia, which was corrected for age, gender and medications used but not for other cardiac risk factors such as smoking, DM and hypertension. However, both a meta-analysis published in 2016 [13] and a UK-based cohort study published in the same year [21] did not find an increased risk of cardiovascular diseases among GCA patients.

Our study, similar to the first three studies, managed to provide support for an increased cardiovascular disease risk in GCA patients. This risk remained valid after stratifying for DM, hypertension, smoking and hyperlipidemia.

Unlike a recent meta-analysis, which demonstrated a significant lower prevalence of DM with a pooled OR of 0.74 in 903 patients with GCA [13], our study, which comprised a population six times larger of GCA patients, found an increased OR of 2.42 for DM. Our findings are actually in accordance with a recent large population-based study from the UK [22], which also noted an increased frequency of DM in patients with GCA (10% in patients with DM vs. 9.6% in controls). This increased prevalence could be the result of the common use of corticosteroids in these patients. The meta-analysis looked at the prevalence of DM before the diagnosis of GCA, while our study could not determine the temporality. Other explanations for these discrepancies can be found in the different data sources and the existing diversity of DM prevalence in different populations.

Our study has several limitations. Using such a large database might include some misclassified GCA patients. However, the CHS database codes were previously validated in many studies [8,16-19,23,24]; moreover, since any misclassification was likely to be non-differential, the results are prone to be biased toward the non-significance and probably are not responsible for the differences found in the study.

This large database allowed us, unlike many other studies, to stratify for traditional risk factors associated with cardiovascular diseases. In addition, this large database provided the opportunity to explore the concurrence of IHD, and a relatively infrequent disease such as GCA, due to its large size.

Another limitation might be due to the fact that we did not look at co-morbidities during different time frames, that is, before the diagnosis was made, during the treatment, and after the treatment. Therefore, we cannot completely ignore the effect of treatment on the results. Corticosteroids, which are the backbone of the pharmacological therapy in this disorder, are practically an integral element of this disease construct and probably also contribute in a way to this association.

CONCLUSIONS

In conclusion, in this large population-based cohort, GCA was found to be independently associated with IHD and risk factors associated with cardiovascular diseases. Attention should be paid by the treating physicians to not overlook this aspect of the disease when managing GCA patients.

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Capsule

Antibodies to cyclic citrullinated peptides in patients with juvenile idiopathic arthritis and patients with rheumatoid arthritis

Antibodies to cyclic citrullinated peptides (anti-CCP) in rheumatoid arthritis (RA) can express the inherently autoreactive gene *V_H4–34*, detected using the rat monoclonal antibody 9G4. Patients with the polyarticular subtype of juvenile idiopathic arthritis (JIA) share some but not all of the features of adult patients with RA. This study was undertaken to compare serologic findings for rheumatoid factor (RF), anti-CCP, and 9G4-expressing anti-CCP in a large JIA cohort with a cohort of adult RA patients. Serum from 88 patients with polyarticular JIA, 29 patients with enthesitis-related arthritis, 38 patients with extended oligoarthritis, 31 adolescent controls, 35 patients with RA, and 30 adult controls were tested for RF, for IgG, IgA, and IgM anti-CCP, and for 9G4-expressing anti-CCP by enzyme-linked immunosorbent assay. Total serum 9G4-positive IgM was also measured.

Of 65 patients with RF-negative polyarticular JIA, 4 (6.2%) were IgG anti-CCP positive. Sera from 20 of 23 patients with RF-positive polyarticular JIA (87.0%), 24 of 35 patients with RA (68.6%), and 1 patient with extended oligoarthritis contained IgG anti-CCP. IgA and IgM anti-CCP levels were lower in the adolescent group ($P < 0.01$). Levels of 9G4-expressing anti-CCP were higher in patients with RF-positive polyarticular JIA than in those with RF-negative polyarticular JIA ($P < 0.0001$). Median levels of 9G4-expressing anti-CCP in patients with RF-positive polyarticular JIA and those with RA did not differ. Expression of 9G4 on serum total IgM was greater in patients with RF-positive polyarticular JIA than other adolescent groups ($P < 0.01$), but similar to adult RF-positive RA. In healthy individuals, 9G4-positive B cells comprise 5–10% of the peripheral blood pool but serum immunoglobulins utilizing *V_H4–34* are disproportionately low. The idiotope recognized by 9G4 was detected on anti-CCP antibodies in > 80% of patients with RF-positive polyarticular JIA. *V_H4–34* usage by anti-CCP in both JIA and RA patients suggest elicitation of these autoantibodies through shared pathogenic B cell selection processes.

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Eitan Israeli

"We're here to put a dent in the universe"

Steve Jobs (1955-2011), American entrepreneur, businessman, inventor, and industrial designer. He was the co-founder, chairman and chief executive officer of Apple Inc.