Cardiovascular risk factors associated with polymyalgia rheumatica and giant cell arteritis in a prospective cohort: EPIC-Norfolk Study

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The study complies with the Declaration of Helsinki. The Norwich District Health Authority Ethics Committee approved the study and all participants gave written informed consent.

Key messages:

- PMR and GCA are strongly correlated with age with disease prevalence set to rise.
- PMR and GCA share common risk factors with vascular disease suggesting a common underlying propensity.
- Pre-existing cardiovascular risk factors need to be taken into account in studies of disease aetiology.

Abstract

Objectives

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are associated with increased risk of vascular disease. However, it remains unclear whether this relationship is causal or reflects a common underlying propensity. The aim of this study was to identify whether known cardiovascular risk factors increase the risk of PMR and GCA.

Methods

Clinical records were examined using key word searches to identify cases of PMR and GCA, applying current classification criteria in a population-based cohort. Associations between cardiovascular risk factors and incident PMR and GCA were analysed using Cox proportional hazards.

Results

In 315,022 person years of follow-up, there were 395 incident diagnoses of PMR and 118 incident diagnoses of GCA which met the clinical definition. Raised diastolic blood pressure (>90 mm/Hg) at baseline /recruitment was associated with subsequent incident PMR (HR = 1.35 (1.01, 1.80) p=0.045), and ever-smoking was associated with incident GCA (HR = 2.01 (1.26, 3.20) p=0.003). Estimates were similar when the analysis was restricted to individuals whose diagnoses satisfied the current classification criteria sets.

Conclusion

PMR and GCA shares common risk factors with vascular disease onset, suggesting a common underlying propensity. This may indicate a potential for disease prevention strategies through modifying cardiovascular risk.

Introduction

Cohort and case-control studies have reported associations between vascular end-points and PMR and GCA, but it remains unclear whether the association is a consequence of disease or reflects a common underlying propensity (1-4). The aetiology of PMR and GCA is unknown but may be explained partly through a mechanism of endothelial dysfunction and chronic inflammation, which in turn may be shared with vascular disease (5, 6).

Few studies have investigated the aetiological contribution of traditional cardiovascular disease risk factors to PMR or GCA disease onset, and their results have been conflicting. Some case-control studies found associations between smoking and GCA, but their findings were not replicated in a recent cohort study from Iceland in which smoking was found to be protective against the onset of GCA (7-10).

The aim of this study was to investigate the aetiological contribution of cardiovascular disease risk factors to incident diagnoses of PMR and GCA, using data from a large community-based cohort study with prolonged follow-up.

Methods

Study population

Individuals were recruited to the European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk cohort study from 35 GP practices across rural, suburban and inner-city areas of Norfolk UK. A total of 25,639 men and women aged 40-79 years were recruited at baseline between the years 1993-1997.

PMR and GCA case assignment and definition

Diagnoses of PMR and GCA were identified amongst participants in EPIC-Norfolk in the following ways: (i) free text questionnaire responses at baseline, 18 months, three, ten and thirteen years follow-up; (ii) linked hospital electronic discharge summaries containing ICD disease codes (iii) out-patient clinic letter key word searches. All cases were diagnosed by either primary or secondary care based physicians, were aged 50 years and over at time of diagnosis and treated with glucocorticoids. This method of case ascertainment has been validated in the Clinical Practice Research Datalink (CPRD). Case assignment was carried out independently by two rheumatologists (MY, RW). All diagnostic tests and case records were scrutinised for all diagnoses and to apply current classification criteria. Analysis was restricted to incident diagnoses of PMR and GCA, namely those cases that developed after the date of enrolment into the cohort. Individuals with coexisting diagnoses of PMR and GCA were classified as having GCA for the purpose of analysis. Participants diagnosed within 12 months of enrolment were excluded from analysis. The end date of the observation period was 31st March 2015.

Covariates

Participants completed validated health and lifestyle questionnaires at inclusion and attended nurse-led health checks at enrolment. These assessments captured information on blood pressure, measures of cholesterol metabolism (triglycerides, high- and low-density lipoprotein, total cholesterol), smoking status, and presence of antecedent diabetes mellitus, and high-sensitivity C-reactive protein (hs-CRP). Blood samples used for measurement of CRP at baseline were centrifuged at 2,100 g for 15 min at 4 °C and then kept frozen in −80 °C freezers until being thawed in 2008. Serum hs-CRP (mg/L) was measured using the Olympus AU640 chemistry analyser (Olympus Diagnostics, United Kingdom).

Analytical models

The association between vascular risk factors and the subsequent risk of PMR and GCA was estimated using hazard ratios in a multivariate Cox proportional hazards regression model. The model included age at recruitment to the cohort, sex, BMI, smoking status, diastolic blood pressure, serum lipid and hs-CRP levels as covariates. A clinically relevant cut-point were chosen for LDL at 3 mmol/L in line with UK guidance. Diastolic blood pressure was dichotomised at 90 mm/Hg to create a category of raised diastolic blood pressure, a recognised risk factor for peripheral arterial disease (11). The ranges for hs-CRP were chosen as <1 mg/L, 1 to 3 mg/L and >3 mg/L be consistent with other published studies including the Women's Health Study (12). There were too few cases of diabetes among the cohort for this to be included as a covariate in the model. A sensitivity analysis was used to investigate the potential influence of misclassification of disease status, with analysis limited to those cases of PMR and GCA which fulfilled the EULAR/ACR criteria for PMR (13) and 1990 ACR criteria for GCA (14). All analyses were carried out using STATA Version 12.1.

Ethical considerations

The study complies with the Declaration of Helsinki. The Norwich District Health Authority Ethics Committee approved the study and participants gave written informed consent.

Results

The study included a total of 315,022 person years of follow up. During this period of observation, there were 395 individuals with incident PMR and 118 with incident GCA. Individuals classified as having GCA, 43 presented with either co-existing or preceding PMR. The characteristics at enrolment of those patients with a final classification of PMR and GCA are shown in Table 1. The mean length of follow-up between enrolment and the diagnosis for PMR was 10.8 years (SD 4.8 years) and for GCA was 11.5 years (SD 4.8 years). Similar proportions of those diagnosed with PMR and GCA were female (PMR 74.4%; GCA 74.6%).

Multivariate modelling accounting for covariates showed raised diastolic blood pressure at time of enrolment to the cohort was associated with subsequent incident PMR, and ever-smoking was associated with incident GCA (Table 2). The strongest associations were with advancing age and the female sex. There was no consistent association with body mass index. There was an increase in the hazard ratio for those individuals with an hs-CRP >3 mg/L at enrolment and subsequent PMR, but the was not statistically significant when restricting to those individuals who met classification criteria.

Model diagnostics including examination of Schoenfeld residuals supported the proportional hazards assumption.

Limiting the analysis to those cases which fulfilled the current classification sets resulted in similar estimates of risk. The estimate for hs-CRP and incident GCA was strengthened (Table 2).

Table 1 . Characteristics of the EPIC-Norfolk cohort at enrolment

	Population who did not develop PMR or GCA (n = 25,147)	PMR meeting clinical definition at subsequent diagnosis (n = 395)	PMR meeting classification criteria at subsequent diagnosis (n = 272)	GCA meeting clinical definition at subsequent diagnosis (n = 118)	GCA meeting classification criteria at subsequent diagnosis (n = 76)
Age at enrolment*	58.9	64.5	64.6	64.6	64.6
Female, n (%)	13,670 (54.4)	294 (74.4)	204 (75.0)	88 (74.6)	57 (75.0)
Never smoker, n (%)	11,443 (45.5)	197 (49.9)	139 (51.7)	47 (39.8)	30 (41.1)
High Blood pressure†, n (%)	3,570 (14.2)	78 (19.8)	52 (19.2)	23 (19.5)	19 (25.0)
Systolic BP (mm/Hg) (SD)	135 (18)	140 (20)	140 (20)	135 (16)	136 (17)
Diastolic BP (mm/Hg) (SD)	83 (11)	84 (12)	84 (12)	82 (11)	82 (11)
Diabetes†, n (%)	581 (2.3)	7 (1.8)	5 (1.8)	2 (1.7)	2 (2.6)
BMI (kg/m^2) (SD)	26.4 (3.9)	26.7 (3.9)	26.3 (3.6)	26.0 (3.7)	25.7 (3.5)
Triglycerides (mmol/L)*	1.5	1.6	1.6	1.6	1.6
HDL (mmol/L) (SD)	1.42 (0.43)	1.49 (0.42)	1.48 (0.40)	1.47 (0.42)	1.47 (0.38)
LDL (mmol/L) (SD)	3.96 (1.03)	4.30 (1.16)	4.30 (1.13)	4.21 (1.09)	4.23 (0.96)
hs-CRP (mg/L) (SD)	3.1 (6.3)	3.8 (7.4)	3.8 (7.6)	3.7 (6.0)	4.3 (7.1)

*medians, otherwise arithmetic means and standard deviations are presented (SD), †Self-reported at baseline questionnaire. Self-reported diagnoses are from baseline questionnaire at time of recruitment. BP – Blood pressure, BMI – Body mass index, HDL – high-density lipoprotein, LDL – Low-density lipoprotein.

Table 2. Vascular risk factors and their association to incident diagnoses of PMR and GCA using multivariate Cox proportional hazard modelling

	PMR	**PMR Classification set**	**GCA**	**GCA Classification set**
Total (n)	395	272	118	76
Age	1.11 (1.09, 1.13) p=<0.0001	1.11 (1.09, 1.13) p=<0.0001	1.12 (1.09, 1.15) p=<0.0001	1.11 (1.07, 1.15) p=<0.0001
Sex (female)	2.11 (1.55, 2.87) p=<0.0001	2.14 (1.55, 2.30) p=<0.0001	2.04 (1.23, 3.40) p=0.006	1.94 (1.03, 3.67) p=0.041
Ever smoking	1.13 (0.87, 1.47) p=0.373	1.11 (0.84, 1.46) p=0.466	2.01 (1.26, 3.20) p=0.003	1.81 (1.02, 3.24) p=0.044
BMI				
<18.5 kg/m2	ref	ref	ref	ref
18.5 - 24.9 kg/m2	0.74 (0.34, 1.60) p=0.441	0.71 (0.33, 1.55) p=0.394	2.04 (0.28, 15.03) p=0.482	1.61 (0.22, 11.99) p=0.643
25.0 - 29.9 kg/m2	0.83 (0.39, 1.79) p=0.637	0.76 (0.35, 1.64) p=0.487	2.22 (0.31, 16.14) p=0.431	1.10 (0.15, 8.20) p=0.923
>30 kg/m2	0.67 (0.29, 1.50) p=0.316	0.58 (0.25, 1.34) p=0.206	1.04 (0.13, 8.54) p=0.967	0.76 (0.09, 6.35) p=0.799
Diastolic Blood pressure >90 mm/Hg	1.35 (1.01, 1.80) p=0.045	1.39 (1.03, 1.88) p=0.033	0.93 (0.54, 1.60) p=0.789	1.29 (0.69, 2.41) p=0.425
LDL >3 mmol/L	1.00 (0.67, 1.50) p=0.998	1.02 (0.67, 1.54) p=0.945	1.07 (0.53, 2.16) p=0.860	2.29 (0.71, 7.44) p=0.167
hs-CRP bands				
<1 mg/L	ref	ref	ref	ref
1 to <3 mg/L	1.31 (0.93, 1.83) p=0.122	1.21 (0.86, 1.71) p=0.269	0.71 (0.40, 1.24) p=0.227	0.65 (0.30, 1.41) p=0.279
>3 mg/L	1.45 (1.00, 2.10) p=0.049	1.33 (0.91, 1.94) p=0.143	1.29 (0.73, 2.28) p=0.378	1.93 (0.96, 3.88) p=0.067

BMI – body mass index, LDL low-density lipoprotein, hs-CPR high sensitivity C-reactive protein.

Discussion

In common with other study designs which have examined the association of risk factors for incident PMR and GCA, our analysis has shown that advancing age and the female sex have the strongest association with the risk of onset of PMR and GCA. Our data also show an association between established cardiovascular risk factors and disease onset: raised diastolic blood pressure (>90 mm/Hg) increases the risk of onset of PMR, and smoking increases the risk of onset of GCA. Increased hs-CRP measured at enrolment was associated with an increased risk for subsequent development of PMR and GCA but the confidence intervals included values with a reduced risk and therefore no definite association can be concluded from these data. In the cohort as a whole, there is association between hs-CRP and the dichotomised diastolic blood pressure variable that that is independent of PMR and GCA, which is consistent with there being aetiological link between vascular disease and inflammation. For BMI the point estimates for risk show a reduced risk for PMR and GCA in those with a BMI of >30 kg/m^2 but did not reach statistical significance. This contrast with a recent study in Sweden that showed a protective effect amongst those with obesity (15).

Previous studies examining the association with cardiovascular factors in these two diseases have produced conflicting results (4) (16). There is also uncertainty as to when the risk operates, and whether vascular disease is a cause or a consequence of PMR or GCA.

A systematic review published in 2012, and a subsequent metanalysis carried out in 2017, concluded that the risk of cardiovascular disease is increased following a diagnosis of PMR (17, 18). In GCA, three separate meta-analyses have assessed risk. from different perspectives, using data from 14 studies. The conclusion was that smoking was a risk factor for GCA onset (19), and that peripheral arterial disease but not cardiovascular disease is increased in individuals following their diagnosis of GCA (2, 20). These analyses included data from a mixture of case-control and cohort designs. All reported substantial heterogeneity.

The issue has also been addressed in large administrative datasets using nested case-control cohort designs. Pujades-Rodriguez *et* al looked at 12 cardiovascular disease presentations in those with a diagnosis PMR, GCA or co-existing PMR with GCA using the CALIBER dataset. CALIBER is a bespoke dataset using participants within Clinical Practice Research Datalink (CPRD) linked to the Myocardial Ischaemia National Audit Project (MINAP), and Hospital Episode Statistics (HES) dataset and the Office for National Statistics (ONS) mortality and social deprivation data. The analysis identified 1,164 patients with GCA and 9,776 patients with PMR (4). No association was found to 12 presentations of vascular disease amongst those with PMR or GCA. Using unlinked data relating to GCA alone from the same data source (CPRD), Li *et al* (16) showed an increased risk for vascular disease. They also found an increased incidence of CVD events prior to the onset of GCA. In both studies, those with PMR or GCA were more likely to have been prescribed blood pressure lowering medication and antiplatelet therapy than controls despite matching on age, sex and GP practice (4) (16).

These large-scale studies based on administrative data did not apply classification criteria to their cases and may have resulted in an underestimate of risk. Using disease end-points as opposed to risk factors for vascular disease potentially limits the power to assess vascular risk. The strength of this study over register-based studies include the detailed case ascertainment, the population-based design, and the length of follow-up.

Our study is limited by the relatively small number of incident cases of PMR and GCA. Further, vascular risk factors were recorded at enrolment which might have led to an underestimate of risk.

In addition, we are unable to assess for treatment of cardiovascular risk factors and how these might have modified risk. A more robust biomarker of early vascular disease would allow these risks to be assessed with greater certainty.

Conclusions

This study shows that cardiovascular risk factors increase the risk of subsequent onset of PMR and GCA and indicate that vascular disease, PMR and GCA share common risk factors. Early characterisation of vascular risk has the potential of reducing the future risk of these diseases amongst a patient population with significant comorbidity.

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