RHEUMATOLOGY

Concise report

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

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Abstract

Objectives. PMR and 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 that met the clinical definition. Raised diastolic blood pressure (>90 mmHg) at baseline/recruitment was associated with subsequent incident PMR [hazard ratio=1.35 (95% CI 1.01, 1.80) P=0.045], and ever-smoking was associated with incident GCA [hazard ratio=2.01 (95% CI 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.

Key words: giant cell arteritis, polymyalgia rheumatica, cardiovascular disease

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> **Rheumatology 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.

CLINICAL SCIENCE

Introduction

Cohort and case-control studies have reported associations between vascular endpoints 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

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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 and 1997. 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.

PMR and GCA case assignment and definition

Diagnoses of PMR and GCA were identified among participants in EPIC-Norfolk in the following ways:

- free text questionnaire responses at baseline, 18 months, 3, 10 and 13 years follow-up;
- linked hospital electronic discharge summaries containing International Classification of Diseases disease codes;
- 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 were treated with glucocorticoids. This method of case ascertainment has been validated in the Clinical Practice Research Datalink. Case assignment was carried out independently by two rheumatologists (M.Y., R.A.W.). All diagnostic tests and case records were scrutinized 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 31 March 2015.

Covariates

Participants completed validated health and lifestyle questionnaires at inclusion and attended nurse-led health cheques at enrolment. These assessments captured information on blood pressure, measures of cholesterol metabolism (triglycerides, high- and low-density lipoprotein, total cholesterol) and smoking status, and presence of antecedent diabetes mellitus and high-sensitivity CRP (hs-CRP). Blood samples used for measurement of CRP at baseline were centrifuged at 2100*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, Hamburg, Germany).

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 was chosen for low-density lipoprotein at 3 mmol/l, in line with UK guidance.

Diastolic blood pressure was dichotomized at 90 mmHg to create a category of raised diastolic blood pressure, a recognized risk factor for peripheral arterial disease [11]. The ranges for hs-CRP were chosen as <1 mg/l, 1–3 mg/l and >3 mg/l to 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 that 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 (StataCorp, College Station, Texas, USA).

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. Among 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 (s.d. 4.8 years) and for GCA was 11.5 years (s.d. 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 female sex. There was no consistent association with BMI. 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 that fulfilled the current classification sets resulted in similar estimates of risk. The estimate for hs-CRP and incident GCA was strengthened (Table 2).

Discussion

In common with other study designs that have examined the association of risk factors for incident PMR and GCA, our analysis has shown that advancing age and 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 mmHg) 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

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, years[a]	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 BP[b], n (%)	3570 (14.2)	78 (19.8)	52 (19.2)	23 (19.5)	19 (25.0)
Systolic BP (s.D.), mmHg	135 (18)	135 (18)	140 (20)	135 (16)	136 (17)
Diastolic BP (s.D.), mmHg	83 (11)	84 (12)	84 (12)	82 (11)	82 (11)
Diabetes[b], n (%)	581 (2.3)	7 (1.8)	5 (1.8)	2 (1.7)	2 (2.6)
BMI (s.D.), kg/m²	26.4 (3.9)	26.7 (3.9)	26.3 (3.6)	26.0 (3.7)	25.7 (3.5)
Triglycerides (mmol/l)[a]	1.5	1.6	1.6	1.6	1.6
HDL (s.D.), mmol/l	1.42 (0.43)	1.49 (0.42)	1.48 (0.40)	1.47 (0.42)	1.47 (0.38)
LDL (s.D.), mmol/l	3.96 (1.03)	4.30 (1.16)	4.30 (1.13)	4.21 (1.09)	4.23 (0.96)
hs-CRP (s.D.), mg/l	3.1 (6.3)	3.8 (7.4)	3.8 (7.6)	3.7 (6.0)	4.3 (7.1)

[a]Medians; otherwise arithmetic means and s.D. are presented. [b]Self-reported at baseline questionnaire. Self-reported diagnoses are from baseline questionnaire at time of recruitment. BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

TABLE 2 Vascular risk factors and their association to incident diagnoses of PMR and GCA

	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 BP >90 mmHg	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

Data are presented as hazard ratio (95% CI) with P-values. BP: blood pressure; hs-CRP: high-sensitivity CRP; LDL: low-density lipoprotein.

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 dichotomized diastolic blood pressure variable that is independent of PMR and GCA, which is consistent with there being an 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 to a recent study in Sweden that showed a protective effect among 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 meta-analysis 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 of PMR, GCA or co-existing PMR with GCA using the CALIBER dataset. CALIBER is a bespoke dataset using participants within Clinical Practice Research Datalink linked to the Myocardial Ischaemia National Audit Project (MINAP), and the Hospital Episode Statistics dataset and the Office for National Statistics mortality and social deprivation data. The analysis identified 1164 patients with GCA and 9776 patients with PMR [4]. No association was found to 12 presentations of vascular disease among those with PMR or GCA. Using unlinked data relating to GCA alone from the same data source (Clinical Practice Research Datalink), Li *et al.* [16] showed an increased risk for vascular disease. They also found an increased incidence of cardiovascular disease 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 general practitioner 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 endpoints as opposed to risk factors for vascular disease potentially limits the power to assess vascular risk. The strengths 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.

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 characterization of vascular risk has the potential to reduce the future risk of these diseases among a patient population with significant comorbidity.

Acknowledgements

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