EXTENDED REPORT

Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis

K Larsson, D Mellström, C Nordborg, A Odén, E Nordberg

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See end of article for authors' affiliations

Correspondence to: Dr Claes Nordborg, Department of Pathology, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden; claes.nordborg@pathology.gu.se

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Objective: To assess female sex hormone related variables in a group of women with biopsy positive giant cell arteritis and a control group.
Methods: 49 women with biopsy positive giant cell arteritis, aged 50 to 69 years at the time of diagnosis, answered a questionnaire on hormonal and reproductive factors. The same questions were answered by a large population of women from the same geographical area in connection with routine mammograms. The results were tested statistically, using logistic regression analysis of each variable adjusted for age, and a multivariate logistic regression analysis including age and the variables which differed significantly between giant cell arteritis and controls.
Results: From the multivariate logistic regression analysis, three independent variables were associated with an increased risk of having giant cell arteritis: smoking and being an ex-smoker (odds ratio (OR) = 6.324 (95% confidence interval (CI), 3.503 to 11.418), p<0.0001); body mass index (a reduction of 1.0 kg/m^2 increased the risk by 10% (OR = 0.898 (0.846 to 0.952), p = 0.0003); and menopause before the age of 43 (OR = 3.521 (1.717 to 7.220), p = 0.0006).
Conclusions: There was a significant association between hormonal and reproduction related factors ?and ?the risk of developing giant cell arteritis in women given the diagnosis before the age ?of ?70. The results suggest a possible role of oestrogen deficiency in the pathogenesis of giant ?cell ?arteritis. To confirm the results, an extended study will be needed, including women older than ?70.

Giant cell arteritis is a chronic inflammatory disorder which mainly affects large and medium sized arteries in women aged 50 years and over.[1] Its aetiology and pathogenesis are incompletely understood. A high incidence in Scandinavia and in communities with a strong Scandinavian ethnic background, as well as the association with HLADR4 antigen, indicates a genetic predisposition.[1] Immunological studies of the vessel wall have revealed local T cell activation, suggesting an antigen driven disease.[2 3] The invasion of T cells and macrophages leads to destruction of the arterial wall, severe thickening of its intima, and stenosis which, in turn, may cause ischaemic damage.[2 3]

The fact that giant cell arteritis predominantly affects elderly women[1] may indicate a pathogenic relation with female sex hormones. Gonadal hormone biosynthesis and adrenal steroidogenesis decline with age, leading to the suppression of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes; shortage of female sex hormones also reduces the responsiveness of the HPA axis.[4–7] As the adrenal steroids are all inhibitors of the immune system, this would augment inflammatory reactions.[5 7] A reduced responsiveness of the HPA axis to inflammatory stimuli has been observed in polymyalgia rheumatica.[5]

There could be epidemiological clues to indicate a link between the metabolism of female sex hormones and the pathogenesis of giant cell arteritis. Our aim in the present study was to compare the occurrence of various hormonal and reproduction related factors in controls and women with biopsy positive giant cell arteritis.

METHODS

Patients

The cases with giant cell arteritis were identified in the files at the department of pathology, Sahlgrenska University Hospital, which is the referral centre for temporal artery biopsies in the Göteborg region. The temporal artery biopsies given a positive diagnosis of giant cell arteritis during the period 1991 to 2000 were identified, and all women aged 50 to 69 years at diagnosis were selected (n = 65). Their inclusion required a clinical diagnosis of giant cell arteritis and a temporal artery biopsy showing signs of chronic arteritis (a mononuclear cell infiltrate in the arterial wall). Seventy per cent of the biopsies contained giant cells. During the year 2003 a questionnaire was sent to these 65 women.

Controls were 10 405 women aged 49 to 69 years who had answered the same questions in connection with routine mammogram screening in the Swedish national programme for the prevention of breast cancer.

Questions

Questions were asked about the following: age at menarche; use of oral contraceptives; parity; length of breast feeding; age at menopause; oophorectomy with or without hysterectomy, and the age when done; use and type of hormone replacement therapy (HRT) for menopausal symptoms; smoking habits (current smoker or smoker for at least six

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; GCA, giant cell arteritis; HLA, human leucocyte antigen; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; HRT, hormone replacement therapy

Table 1 The variables not contributing significantly to the discrimination between giant cell arteritis and controls

Variable	GCA	Controls	p Value
Age at menarche (years)	13.4	13.7	0.3120
Number of children born	2.12	2.01	0.5596
Use of contraceptive pill (%)	32.7	44.9	0.1103
Oophorectomy (%)	18.4	13.8	0.4602
HRT (%)	38.8	42.0	0.7478

GCA, giant cell arteritis; HRT, hormone replacement therapy.

months; age when started smoking; age at cessation of smoking; number of cigarettes smoked a day and whether smoke inhaled); and body mass index (BMI; body weight (kg)/height^2 (m) at the time of menopause).

Statistical methods

A difference in age distribution within the 49 to 69 year age range was observed between the patients with giant cell arteritis and the control population. All the analyses were therefore adjusted for age.

As a first step, logistic regression analysis, with age as an independent variable, was used to test differences between patients with giant cell arteritis and controls for the set of variables in the questionnaire. Variables showing a significant difference were investigated further, using multivariate logistic regression analysis. In addition to age, the variables included in the latter analyses were smoking, BMI, menopause before the age of 43, and duration of breast feeding. The p values given in table 1 were determined by Fisher's permutation test,[8] which includes Fisher's exact test as a special case, and the p values of table 2 were calculated using the approximate normal distribution of the estimated β coefficients.

The study was approved by the local research ethics committee at the Medical Faculty, Göteborg University (S 278-01).

RESULTS

In all, 65 biopsy positive women aged 50 to 69 years were identified during the study period (1991 to 2000). In 2003, 49 of these (mean age 64.1 years, range 52 to 69, median 65) agreed to answer the questionnaire. Five of those who did not reply had died and two women had dementia. Another seven women did not answer the questionnaire despite repeated efforts to contact them. Two women did not wish to participate. The mean age of the 16 drop outs was 64.8 years (range 51 to 69; median 66).

Five of the nine variables did not differ between the giant cell arteritis group and the controls (table 1), whereas four factors differed significantly: smoking (current smokers or ex-smokers) was more common, the average BMI was lower, menopause before 43 years was more common, and the average duration of breast feeding was longer. These variables were analysed further, using multivariate logistic regression analysis. Independently of the others, each was associated with a significantly increased risk of having giant cell arteritis. Thus, for women who were smokers or ex-smokers or who had menopause before 43 years of age, there was an increased risk of having giant cell arteritis. Likewise, this risk increased by 10% when BMI was reduced by 1.0 kg/m^2 (one unit, corresponding to approximately 3.0 kg body weight in the present population). Finally, each month of breast feeding incurred a 2.9% increased risk of having giant cell arteritis (table 2). Because of the rareness of giant cell arteritis, the odds ratios presented here almost coincide with hazard ratios.

DISCUSSION

Our study showed a significant association between biopsy positive giant cell arteritis and four factors related to female sex hormones and reproduction, namely early menopause, smoking, low BMI, and breast feeding.

Menopause before the age of 43 was associated with an increased risk of having giant cell arteritis. Likewise, each month of breast feeding caused a minor increase in the risk. Early menopause and extended breast feeding imply longer periods of reduced influence from female sex hormones.[9–11] The present results thus suggest a relation between low female sex hormone production and the risk of developing giant cell arteritis.

Shortage of female sex hormones and the suppression of the HPG axis might reduce the responsiveness of the HPA axis in biopsy positive giant cell arteritis; while high levels of oestrogens potentiate the response of the HPA axis, low levels blunt the system.[4–7] The reduced responsiveness of the HPA axis to inflammatory stimuli has been observed in polymyalgia rheumatica.[5]

Interleukin 6 (IL6) and adrenocorticotropic hormone (ACTH) act synergistically to stimulate the direct release in corticosterone from the adrenal gland.[12] However, despite high serum levels of both IL6 and ACTH, serum cortisol is low in polymyalgia rheumatica, even before the initiation of corticosteroid treatment, which indicates that in this disorder a reduction in the HPA axis may augment the inflammatory process.[5] It remains to be shown if this is also the case in biopsy positive giant cell arteritis. The relatively greater age of the patients with giant cell arteritis might add further to a suppression of the HPA and HPG axes, as gonadal hormone biosynthesis and the adrenal steroidogenesis decline with age.[5 7]

In the present study, there was no significant difference between the giant cell arteritis patients and the controls with respect to parity. Duhaut *et al*[13] found fewer pregnancies among patients with giant cell arteritis than among controls, suggesting that the hyperoestrogenic state of pregnancy may protect the arterial wall.[14] While in the French study, the control group and the index patients came from different regions, our patients and controls were from the same geographical area.

Table 2 Multivariate analysis and risk factors

Variable	β	SE	p Value	OR	95% CI
Smoking (never = 0; now or before = 1)	1.84437	0.30144	<0.0001	6.324	3.503 to 11.418
BMI	−0.10787	0.03006	0.0003	0.898	0.846 to 0.952
Menopause before 43 y (no = 0; yes = 1)	1.25875	0.36641	0.0006	3.521	1.717 to 7.220
Breast feeding (months)	0.02827	0.01278	0.0270	1.029	1.003 to 1.055

BMI, body mass index; CI, confidence interval; OR, odds ratio; SE, standard error; y, years.

Low BMI was associated with an increased risk of having giant cell arteritis. A low BMI implies a reduction in adipose tissue, which will in turn have an impact on oestrogen synthesis. Oestrone, which is the principal oestrogen in postmenopausal women, is formed by the conversion of adrenal androstendione, mainly in adipose tissue.[15] Moreover, thinness has been associated with higher levels of sex hormone binding globulin (SHBG) and lower levels of serum oestrone and oestradiol than those found in heavier women.[16] However, in the present study the serum oestrogen concentrations were not measured.

Smoking proved to be as strong a risk factor for giant cell arteritis as it is for pulmonary carcinoma. This is in accordance with two previous studies.[17 18] The anti-oestrogenic effect of cigarette smoking appears to be related to an increase in the hepatic transformation of oestrogens into inactive catechols.[19] This may in turn be related to the induction of oestrogen metabolising cytochrome P450 isoenzymes.[20] Furthermore, nicotine acts as an aromatase inhibitor.[21] Finally, smoking reduces BMI and the oestrone synthesis in adipose tissue, and female smokers experience menopause two to three years earlier than non-smokers.[22 23] However, according to the multivariate analysis, smoking was a significant risk factor, independent of BMI and age at menopause.

In addition to oestrogen related effects, smoking might directly influence the arterial wall in various ways. Its noxious influence on the endothelium and the increased risk of atherosclerosis are well documented.[24–26] However, there are several arguments against an aetiological or pathogenic relation between atherosclerosis and giant cell arteritis. First, atherosclerosis is extremely rare in the temporal arteries. The two disorders also differ in terms of their distribution in the arterial tree. Whereas giant cell arteritis mainly affects the thoracic part of the aorta, atherosclerosis shows a preference for the abdominal segment. Second, their histology is different. Atherosclerosis involves intimal lipid accumulation, associated with a chronic inflammatory reactions with foam cells, fibrosis, and calcification of lipid-rich necrotic atheromatous plaques. The intimal thickening in giant cell arteritis is strictly associated with, and induced by, the inflammatory reaction.[27 28] Lipid accumulation and foam cells are not part of the process. Finally, its epidemiology is different, especially when it comes to the sex distribution.[1]

The average age at diagnosis of giant cell arteritis is around 70 years in most large series.[1] In the present study we chose a somewhat younger population of women (median age 65) to match the age of the controls. Thus our results may not be applicable to the whole population of patients with giant cell arteritis. Furthermore, a case–control study of this kind may be confounded by selection bias. However, for the investigated period, *all* 50 to 69 year old biopsy positive women in Göteborg were identified, and the median age and age range of the drop outs were very close to those of the women included.

Recall bias was probably minor in the present study. After answering the questions in writing, each patient was contacted by phone. They did not hesitate over facts asked for. The relatively young age of the cohort was probably favourable for recall of the oestrogen related factors asked about in the questionnaire. The oldest patient was 81 at the time of the study. One additional explanation may be that the questions concern events that are central in a woman's life. The fact that the corticosteroid treatment in giant cell arteritis leads to weight gain may explain why the patients were well aware of their body weight.

In conclusion, this study shows that smoking, low BMI, early menopause, and lactation are independent risk factors for developing giant cell arteritis. However, to ensure the generalisability of the results, patients of all age groups must be studied. Whether our findings reflect oestrogen deficiency is an intriguing question that merits further investigation.

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Authors' affiliations

K Larsson, Department of Rheumatology, Sahlgrenska University Hospital, Göteborg, Sweden
D Mellström, Centre for Bone Research at the Sahlgrenska Academy, Department of Geriatrics, Sahlgrenska University Hospital
C Nordborg, Department of Pathology, Sahlgrenska University Hospital
A Odén, Department of Pathology, Sahlgrenska University Hospital
E Nordborg, Department of Rheumatology, Sahlgrenska University Hospital

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