Giant Cell Arteritis: Pathogenetic and Epidemiological Aspects

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I. Early menopause, low body mass index and smoking are independent risk factors for developing giant cell arteritis. Larsson K, Mellström D, Nordborg C, Odén A, Nordborg E. Ann Rheum Dis 2006 Apr;65(4):529-32

II. Expression of the class I interferon-related MxA protein in temporal arteries in polymyalgia rheumatica and temporal arteritis. Nordborg C, Larsson K, Åman P, Nordborg E. Scand J Rheumatol 2009 Mar-Apr;38(2):144-8. (iFirst Article 2009:1-5)

III. Stereological study of neovascularization in temporal arteritis. Nordborg C, Larsson K, Nordborg E. J Rheumatol 2006;33:2020-2025

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ABSTRACT

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Giant cell arteritis (GCA) is a chronic inflammatory disorder of medium-size and large arteries which affects people aged 50 years or older with a female preponderance. The two different expressions of GCA are temporal arteritis (TA) and polymyalgia rheumatica (PMR). In recent years, new information about the immunology and morphology of GCA has emerged. However, many details of its pathogenesis remain to be clarified.

The aims of this thesis was **a)** statistically to investigate a possible connection between GCA and female sex hormone-related factors, **b)** immunocytologically to assess the expression of interferon (IFN) type 1-associated Myxovirus resistance protein A (MxA protein) in PMR and TA, and **c)** stereologically to illustrate the neovascularisation in the inflamed arteries.

a) Fourty-nine women, aged 50 to 69, with a biopsy-positive diagnosis of GCA replied to a questionnaire regarding estrogen-related factors. As controls served 10,405 age-matched women from the same region, who answered the same questionnaire in connection with mammography screening. Logistic regression analysis, with age as an independent variable, revealed four significant differences. These were further investigated, using multivariate logistic regression analysis. The investigation revealed four independent risk factors for developing GCA; menopause before the age of 43, smoking, low body mass index (BMI) and breast-feeding.

b) The immunocytochemical expression of the IFN type 1-related MxA protein was mapped in temporal artery biopsies. Non-inflamed biopsies from 11 PMR patients were compared with arteries from 13 patients with other diagnoses. The morphology of arteries from four patients with full-blown temporal arteritis were studied separately. MxA protein expression was significantly more common in vessel walls and vascular dendritic cells in PMR than in controls. The MxA expression in the inflamed arteries was found in smooth muscle cells remote from inflammation. The results indicate that arterial smooth-muscle and dendritic cells from patients with GCA are under influence of IFN type 1.

c) Twenty-one temporal artery biopsies with different inflammatory degrees of GCA were immunocytologically stained for the detection of the endothelium-related CD34 marker. The degree of inflammation was semiquantitatively assessed. A stereological examination of the relation between endothelial surface and tissue volume (surface density) was performed on calibrated photographic enlargements of CD 34-stained arterial cross sections. The degree of vascularisation as well as the degree of inflammation was greatest in the adventitia, smaller in the media, and smallest in the intima. The correlation between the degree of vascularisation (surface density), and the degree of inflammation was assessed in the different layers of the vessel wall. A significant correlation between the two was found in the media and outer and inner halves of the intima. An extended investigation of the intima (n:27) revealed prominent circular microvascular intimal plexa in 16 of the cases. Eight of these lacked connection with microvessels in the media, and another 8 showed only few single connections. There were no connections with the luminal endothelium.

Conclusions. **a)** Four independent estrogen-related risk factors for developing GCA were detected, namely early menopause, smoking, low BMI, and breast-feeding. The results may indicate a link between estrogen deficiency and GCA. However, the study included relatively young women, aged 50 to 69. To generalise the results, GCA patients of all age groups should be studied. **b)** The significant expression of the MxA protein in non-inflamed temporal arteries in PMR indicates that they are under the influence of IFN type 1, and that IFN type 1 might play a pathogenetic role in GCA. **c)** Stereology may be used for the assessment of vascularisation in GCA. The degree of neovascularisation was related to the degree of inflammation. Isolated vascular plexa in the intima may indicate an alternative mechanism of neovascularisation in terms of recruitment of vascular stem/progenitor cells.

Key words: Giant cell arteritis, Temporal arteritis, Polymyalgia Rheumatica, Estrogen, Immunocytochemistry, MxA protein, IFN type 1, Stereology, Neovascularisation.

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