Editorial

Peripheral arterial disease in polymyalgia rheumatica

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Abstract

Patients with polymyalgia rheumatica have been shown to have an increased risk of peripheral arterial disease on longitudinal follow-up. Possible explanations for this include premature atherosclerosis related to chronic inflammation, as with other inflammatory rheumatological conditions. Alternatively, polymyalgia rheumatica can be associated with vasculitis, even in the absence of clinical giant cell arteritis, and peripheral vascular disease may represent subclinical vasculitis. Further work is required to elucidate the reasons for this increased risk. Currently, it would remain reasonable to aggressively control modifiable atherosclerotic risk factors.

Introduction

Warrington and colleagues report an increased risk of peripheral arterial disease (PAD) in patients with polymyalgia rheumatica (PMR) compared with matched controls [1]. They found that 38 out of 353 PMR patients developed PAD versus 28 out of 705 control subjects over a median follow-up of 11 years (hazard ratio adjusted for conventional cardiovascular risk factors = 2.5, 95% confidence interval = 1.53 to 4.08). The same centre previously reported an increased likelihood of coronary and cerebrovascular disease in PMR [2]. The authors speculate that possible explanations for this are premature atherosclerosis related to inflammation, or the presence of subclinical vasculitis.

Premature atherosclerosis and autoimmune inflammatory disease

An increased risk of cardiovascular disease is well established in inflammatory rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis [3], over and above the risk explained by conventional cardiovascular risk factors. This increase appears to be related to chronic inflammation, with elevated levels of C-reactive protein associated with increased risk of cardiovascular disease, including PAD [4]. Atherosclerosis itself can be explained as an inflammatory process, with proinflammatory cytokines key in the development of endothelial dysfunction and the progression of atheromatous lesions.

Homocysteine has been implicated in the development of atherosclerotic disease in the general population, and in patients with systemic lupus erythematosus and rheumatoid arthritis. Levels of homocysteine have also been found to be elevated in PMR [5].

Although Warrington and colleagues found no correlation between PAD and PMR-related disease characteristics or the erythrocyte sedimentation rate at diagnosis, patients with PMR were at 2.5-fold increased risk even when adjusted for conventional risk factors for atherosclerosis [1]. This lack of association may simply reflect the limited statistical power of the study, which is acknowledged by the authors. Symptomatic PAD was an infrequent occurrence, seen in 38 out of 353 patients with PMR and in 28 out of 705 control patients. Atheroma mediated by chronic inflammation may still explain the elevated PAD risk since chronic inflammation in PMR would not be captured by the erythrocyte sedimentation rate at diagnosis. A previous study from the Mayo Clinic demonstrated an association between sustained elevation in the erythrocyte sedimentation rate (>3 recorded measurements >60 mm/hour at least 30 days apart) and cardiovascular death in rheumatoid arthritis. Measures such as this or the time spent with clinically active disease would better reflect chronic inflammation [6]. C-reactive protein may be a better marker of cardiovascular risk in PMR, as this association is well demonstrated in other chronic diseases, both rheumatological and non-rheumatological.

In the related condition of giant cell arteritis (GCA), increased cardiovascular mortality was associated with both the erythrocyte sedimentation rate and the steroid dose, suggesting proatherogenic effects of high-dose glucocorticoids and/or

GCR = giant cell arteritis; PAD = peripheral arterial disease; PMR = polymyalgia rheumatica.

uncontrolled inflammation [7]. The higher PAD risk in PMR found by Warrington and colleagues may also be explained by steroid use, although lower doses and a smaller sample size may have led to the observed lack of association [1]. This lower steroid dose may explain why, in a previous study from the same centre, glucorticoid use was not associated with increased risk of coronary, peripheral vascular or cerebrovascular disease (hazard ratio = 0.58 to 0.85) [8].

Subclinical vasculitis

Arteritis has not been demonstrated in premature cardiovascular disease in systemic lupus erythematosus or rheumatoid arthritis on postmortem examination [3]. Arteritis remains a possibility, however, in PMR and GCA. A study of biopsy-proven GCA demonstrated no increase in carotid intimal thickness, so atherosclerosis alone does not explain the increased cardiovascular mortality seen in GCA [9].

Although Warrington and colleagues did not find that the presence of clinical GCA correlated with PAD, the sample size was small. Cranial GCA has also been shown to be negatively associated with large vessel involvement [10]. Moosig and colleagues demonstrated large artery (aortic, subclavian, and axillary) uptake on positron emission tomography in 12 out of 13 patients with active PMR, but no clinical evidence of GCA [11]. Proinflammatory macrophage and T-cell-derived cytokine mRNA profiles similar to that of GCA have been found in histologically normal temporal artery specimens from patients with isolated PMR [12]. Subclinical ongoing large vessel vasculitis can therefore occur and may contribute to the increased risk of PAD in isolated PMR.

Conclusions

The interesting findings of Warrington and colleagues add further weight to the association between vascular disease and inflammatory rheumatological conditions. In PMR this possibly relates to inflammation-related atherosclerosis, or to subclinical arteritis. Further longitudinal observational cohort studies including structured documentation of disease activity, cumulative steroid dosages, and C-reactive protein levels are required to unravel the multiplicity of factors and interactions that may contribute to adverse vascular events in this condition.

Competing interests

The authors declare that they have no competing interests.

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