Genetic and environmental factors in polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is a disease that rheumatologists feel confident in recognising in their daily practice. In the classic form, its diagnosis is straightforward and standard corticosteroidal treatment usually yields excellent results, at least in the first months. In contrast with the feeling that PMR is a disease that can be readily treated, the aetiology and pathogenesis are still obscure. Unlike several other forms of rheumatic disease, we do not know what the target of inflammation is in PMR. The synovial membrane is the most probable candidate as synovitis has been demonstrated by sonographic[1] and immunohistochemical[2] methods. In addition, the frequent occurrence of peripheral arthritis in patients with PMR further supports this possibility.[3] Synovitis is mild and patchy in extent, which does not explain the amount of inflammation disclosed by symptoms and laboratory tests. The skeletal muscle was considered the main site of inflammation by Barber[4] who coined the name 'polymyalgia rheumatica'. Although this theory has been discarded for a long time, recent descriptions of the association between PMR and mitochondrial myopathy[5] and of corticosteroid responsive electromyographic abnormalities[6] in patients with PMR have reawakened interest in the role of skeletal muscles. Vasculitis is another attractive possibility because it could comprise PMR and giant cell arteritis (GCA) under a common pathogenesis. The evidence for active vasculitis in biopsy specimens from patients with PMR, however, is scanty. There are also new data that point to bursae as the principal site of inflammation.[7] The large surface of synovial tissue in bursae around glenohumeral joints could explain the amount of inflammation seen in PMR.

The main areas of research in PMR aetiopathogenesis are immunology, genetics, and the environment.

Immunology

The concept that PMR cannot be an autoimmune disease because of the lack of autoantibodies has been challenged by the finding of anti-lamin B2 antibodies specific for the C terminus in PMR patients.[8] Other findings that suggest involvement of the immune system are the decrease of circulating CD8+ lymphocytes,[9] which return to normal values with remission, the increased concentration of soluble CD8,[10] soluble interleukin 2 (IL2) receptors[11] and intercellular adhesion molecule 1,[12] and the pattern of cells infiltrating the synovial membrane. These are mainly CD4+ lymphocytes and macrophages with intense expression of HLAII class antigens.[2] This pattern, which is very close to that seen in GCA,[13] is highly suggestive of efficient antigen presentation and of consequent antigen driven immune inflammation.

Genetics

The role of genetic predisposition in PMR has been suspected because of the geographical distribution of the disease. The incidence is higher in northern Europe than in the south. The same trend can be observed in the US, with a high incidence in Minnesota,[14] a state with a large population of Scandinavian stock, and low incidence in the south. PMR is virtually absent in Africans and African-Americans. This geographical distribution is similar to that seen for rheumatoid arthritis (RA) and multiple sclerosis, which share with PMR an association with HLA DR4. Weyand *et al* showed however that PMR and GCA, which are genetically related, differ from RA.[15] PMR and GCA share the associated sequence polymorphism (DYF) encoded by the second hypervariable region of the HLA-DRB1 gene. In contrast, RA is linked to a sequence motif in the third hypervariable region of DRB1 alleles.[15] Recent findings from the UK, however, have shown similar HLA profiles in patients with PMR and in those with RA.[16] Further support to the genetic component of PMR has been given by Johansen *et al* who have shown that CD8+ cells depletion is present also in relatives of patients with GCA or PMR.[17]

Environment

The geographical trend described above could also suggest environmental factors. Infectious agents have been extensively studied because the acute onset of PMR and its systemic symptoms resemble those of an infectious disease. In addition, an increased frequency of trivial infections before the onset of GCA has been shown in a series of patients.[18] Serological reports have given poor results,[19] however, except for an increased prevalence of antibodies to respiratory syncytial virus and to adenovirus observed in Italy.[20] Although these findings suggest that trivial infections may trigger PMR in elderly subjects, molecular biology techniques should be applied to provide direct evidence of infection in the affected tissues.

Epidemiological data regarding PMR and GCA also suggest an infection. The cyclic pattern observed in the incidence of GCA in Rochester is in agreement with the theory of population immunity after infection.[21] A similar study performed in Denmark found correlations between the incidence peaks of PMR and epidemics of parvovirus B19, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* infections.[22] Parvovirus B19 is an interesting candidate for the aetiological agent of PMR/GCA because it has been involved in the aetiopathogenesis of other vasculitides such as Kawasaki syndrome,[23] Wegener's granulomatosis and polyarteritis nodosa.[24] In addition, P antigen, the receptor of parvovirus B19 on erythrocytes, is present also on endothelial cells.[25]

Environmental factors could help explain why PMR is a disease of the elderly and why the associated GCA is preferentially located in the temporal artery. O'Brien and Regan have proposed that long term exposure to sunlight, including infrared and ultraviolet radiation, can change the internal elastic lamina of the arteries making it antigenic.[26] These authors found lesions similar to those observed in GCA in the temporal and posterior ciliary arteries of aged subjects.[27] Alternatively, normal aging of the arteries may predispose to an autoimmune reaction against arterial constituents. In addition, aging of the immune system, including a comparatively deficient cortisol response to stress, may be the cause of the persistent inflammation seen in PMR.[28] Although the elastic tissue could be an ideal antigen for the autoimmune response in PMR and GCA, there is no experimental evidence for this hypothesis.

On the other hand, the role of sun exposure is supported by the finding of a seasonal trend in the onset of PMR[29] and GCA[30] and of its association with the risk for PMR.[31] However, a seasonal trend was not observed in Rochester.[14] The major objection to this hypothesis is that epidemiological studies have shown a higher incidence of PMR in northern countries where sun radiation is less intense. A possibility is that sun exposure acts in combination with genetic predisposition. Skin sensitivity may also modulate the effect of sun radiation on dermal arteries. In fact, people of Nordic origin usually show a light complexion, which is associated with a very low defence from sun radiations. This hypothesis would also explain the predilection of GCA for the temporal artery because this superficial artery of the scalp is directly exposed to light.

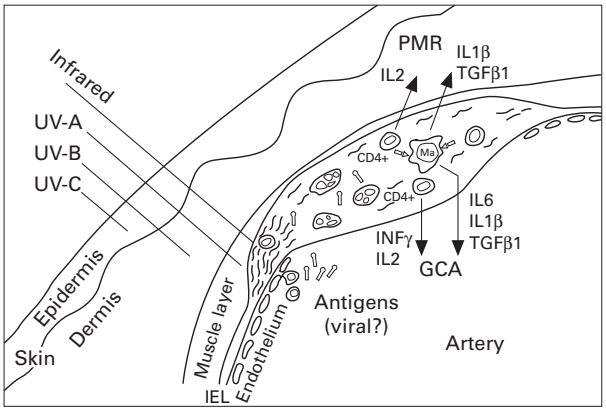

Figure 1 Sun radiation of both the infrared and ultraviolet A types damages the internal elastic lamina (IEL) of superficial arteries facilitating the localisation of an unknown aetiological agent (viral proteins or degenerated vascular components?). This antigen is presented by macrophages (Ma) and is recognised by CD4+ lymphocytes in the context of class II MHC molecules. Macrophages and lymphocytes are stimulated to produce increased amounts of cytokines, which can lead to PMR or to GCA, depending on their pattern. This mechanism is facilitated by predisposing factors, such as old age, female sex, and specific HLA-DRB1 alleles.

Based on the immunological, genetic, and environmental data mentioned above, the following mechanism could be hypothesised for the aetiopathogenesis of PMR (fig 1). In a predisposed subject because of old age, female sex, and specific HLA-DRB1 alleles the superficial arteries may be damaged by atherosclerosis or sun induced elastic fibre degeneration. The damaged elastic layer, and possibly the synovial membrane, may be reached by viral antigens. Interestingly, several viruses, including adenovirus, may persist for a long time in a latent form and can be reactivated by physical stimuli such as heat.[32] Recognition of the still unknown antigen by TH1 CD4+ lymphocytes after class II MHC mediated presentation by macrophages leads to cytokines production. Activated CD4+ lymphocytes and macrophages produce an increased concentration of IL2, interferon γ, and of IL1β, IL6, and transforming growth factor β1, respectively. Interestingly, interferon γ has an antiviral activity and its production is increased after viral infection. An incomplete pattern of cytokines (IL1β, transforming growth factor β1, IL2) is associated with a prevalently extravascular disease typical of PMR whereas the addition of IL6 and interferon γ could represent an amplification loop leading to arteritis.[13]

The scheme reported in figure 1 is an attempt at combining the genetic and environmental hypotheses. Both of them seem to be at work in PMR as confirmed by case reports describing the disease in close relatives[33] or in non-consanguineous subjects living in the same environment.[34] However, the relative weight of genetic and environmental factors may differ in different geographical areas. It is obvious that many pieces of the puzzle are still missing. The temporal artery seems to be the site of an active immunological reaction in both GCA and PMR but the mechanisms leading to the articular or periarticular involvement of PMR are still unclear. Further epidemiological studies are needed on the correlation between incidence of PMR and epidemics of infectious diseases, collection of microbiological and HLA data of family cases, and the demonstration of bacterial or viral antigens in the affected tissues.

MARCO A CIMMINO

Cattedra di Reumatologia, Dipartimento di Medicina Interna, Università di Genova, Genova, Italy

Correspondence to:
Dr M A Cimmino, Cattedra di Reumatologia, DIMI, Viale Benedetto XV 6, 16132 Genova, Italy.

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