Editorial

The aetiology of psoriatic arthritis

There is little question that psoriatic arthropathy (PsA) is a poorly studied entity. At the recent 64th American College of Rheumatology meeting, abstracts relating to PsA were out numbered five to one by studies on systemic lupus erythematosus SLE, a condition of similar prevalence. The concept of PsA is not universally accepted, and even among those who accept the concept there is no internationally agreed definition or diagnostic criteria. For example, while Moll and Wright’s [1] original definition described PsA as ‘an inflammatory arthritis associated with psoriasis and usually negative for rheumatoid factor’, some groups have excluded patients who are positive for rheumatoid factor [2].

It is accepted that psoriasis and inflammatory arthritis coexist more frequently than would be expected by the coincidence of two common conditions, i.e. psoriasis and rheumatoid arthritis (RA) [3, 4]. The explanation for this increased association has been the subject of much debate. The commonest explanation is that there is a distinct entity called psoriatic arthropathy. It should, however, be remembered that alternative explanations for this association do not necessarily invoke the presence of a distinct syndrome. Psoriasis may be a risk factor for inflammatory arthritis. Also, a common genetic or environmental trigger may result in the expression of psoriasis and inflammatory arthritis and thus again explain the increased association. When dealing with this concept of a ‘disease within a disease’ it is important to bear these alternative explanations in mind. Are there distinct clinical features of PsA that distinguish it from a coincidence of psoriasis and inflammatory arthritis? There are several aspects which are generally accepted as occurring in PsA that help to distinguish it from rheumatoid, though not from other forms of inflammatory, arthritis. Such features include distal interphalangeal (DIP) joint involvement, asymmetry, inflammation in a ray pattern and dactylitis. These features do not appear to be absolute. Asymmetry, for example, is not helpful [5]. There have only been a few community-based studies that have attempted to quantify the distinctive features of this condition. In the Norfolk arthritis register (a population-based inception cohort of patients with inflammatory polyarthritis), the features of arthritis in 51 consecutive patients with psoriasis were compared with those in 915 patients with inflammatory arthritis and no psoriasis [6]. In this study, many features were similar but patients with psoriasis were more likely to be male and significantly less likely to be positive for rheumatoid factor and hence less likely to have erosions at 1 yr. There was also a trend towards more frequent DIP joint involvement. A larger study with longer follow-up is now planned using this cohort, which may shed some further light on these differences. Van Romunde et al. [7] also found that in subjects with seronegative arthritis and psoriasis DIP joint involvement was more common than in a comparative group without psoriasis. With regard to pathogenesis, several studies of synovial fluid cytokine profiles indicate differences between PsA and RA that are largely quantitative rather than qualitative [8, 9] and may reflect variability in patient selection and the intensity of the inflammatory response rather than differing pathogenic mechanisms. In contrast, others have noted a distinct vascular pattern in PsA compared with RA synovium [10], and on synovial biopsy specimens there are important differences in cytokine and growth factor profiles which may point to differences in the pathogenesis of these two processes [11, 12].

This lack of a precise understanding of what distinguishes PsA clinically and pathologically can lead to problems when considering aetiology. Studies need to address whether there is a separate aetiology for PsA over and above that observed for the component parts, i.e. psoriasis and arthritis. Such studies require appropriate controls but rarely have psoriasis and inflammatory polyarthritis controls been included in the same study. The factors that have been considered in the aetiology of PsA to date include genetic and environmental risk factors, principally infective, traumatic and psychological triggers.

Older studies suggest a familial recurrence risk of about 40 for PsA, which is ten times that reported for either RA or psoriasis alone [13, 14]. Recent studies have also suggested excessive paternal transmission of PsA. Patients with PsA who have an affected parent are more likely to have an affected father than mother. Similarly, offspring of an affected father are more likely to develop PsA than offspring of an affected mother [15]. The exact explanation for this remains uncertain.

There have been many studies, which have focused on comparing HLA class I alleles between patients with PsA and population controls. These studies have shown an association with HLA B13, B17 and CW6 [16], and molecular typing has found that the CW6 association is with the CW‘0602 allele, which is also found in patients with psoriasis alone [17]. In studies in which psoriatic arthritis has been compared with psoriasis controls as well as population controls, many of the associations with HLA class I alleles are no longer observed and the associations with several of these alleles are weaker in PsA than in psoriasis alone [16, 18, 19]. In two studies of linkage analysis in psoriasis affected sibling pair families, linkage to 6P(HLA) has been found. In both studies, it was more significant in families without a complicating arthropathy [20, 21]. In contrast, HLA B27 and B7 have been associated with PsA independently of psoriasis [18, 19]. The HLA B27 association
is particularly strong with sacroiliitis but others have also suggested an association with DIP joint disease [16]. An association between peripheral symmetrical arthritis and HLA DR4 has also been described, but whether this represents an overlap with rheumatoid arthritis is unclear [17]. A small number of studies have looked at other genes within the MHC in PsA. An association of MICA (class I MHC chain-related gene A) has been found in PsA independently of psoriasis [22]. Others have also found an association between PsA, juvenile-onset psoriasis and the −238 TNF-α promoter polymorphism [23]. Conflicting results have been reported for polymorphism in the immunoglobulin heavy chain gene, and it is unclear whether the association is with PsA or psoriasis alone [24, 25].

Therefore, familial aggregation suggests a significant genetic contribution to the aetiology of PsA, which is stronger than that observed for psoriasis alone and RA alone. This suggests distinct genetic aetiological factors for PsA. To date, immunogenetics has confirmed the association of PsA with genes known to be associated with psoriasis (e.g. HLA Cw6) and with arthritis (e.g. HLA B27), with few unique associations of HLA with PsA being described. It is therefore by no means clear whether HLA contributes significant additional susceptibility to PsA, and the additional genetic contribution to PsA is likely to lie elsewhere.

In general, while genetic studies to date have revealed limited data to suggest a distinct aetiology, there are several environmental triggers that appear to have a more distinctive aetiological contribution. The role of microorganisms has been evaluated in several small studies. Circumstantial evidence to suggest that infection may be important in the aetiology of PsA includes the fact that other forms of seronegative arthropathy are often associated with infectious agents. In addition, guttate psoriasis is well recognized following streptococcal infection. Infection, therefore, may be a common aetiological factor in both psoriasis and an associated inflammatory arthritis. Alternatively, patients with psoriasis may have increased susceptibility to develop arthritis on exposure to infection. Several lines of evidence suggest that bacterial or viral agents may be associated with PsA. Circulating levels of an adenylate acid polymer (2-5A), a potential marker of viral replication, have been found to be higher in patients with PsA compared with RA and healthy controls [26]. With regard to particular microorganisms, Taglione et al. [27], in an Italian population, found antibodies to hepatitis C virus in 12% of patients with PsA compared with 6% of controls with uncomplicated psoriasis. There have been several case reports and case series suggesting an association between HIV infection and both psoriasis and psoriatic arthritis. A recent study from Zambia, where HIV infection is endemic, found that 94% of consecutive patients with PsA had evidence of HIV infection compared with the background population frequency of 30% [28]. Vasey et al. [29] also noted that antibodies to antideoxyribonuclease β, a group A streptococcal endotoxin, were found in 50% of serum from patients with PsA; this was double the prevalence seen in psoriasis and RA controls. Overall, these studies do suggest that several microorganisms are associated with PsA more strongly than with psoriasis and/or RA. The evidence to date suggests that it may be a common response to a variety of infective triggers rather than a response to a single organism. The almost universal finding of HIV infection in an African population with PsA may reflect the fact that this is the most likely viral trigger for PsA that will be encountered in that population. Alternatively, HIV infection may coexist with, or increase the likelihood of other infections. It is also possible that HIV infection serves to alter the T-cell balance in favour of developing PsA.

The role of trauma in PsA has also been the subject of some interest, and it is intriguing to speculate that the Köbner phenomenon, a recognized feature of skin psoriasis, may also occur in peripheral joints. Several case reports of PsA developing following specific trauma have been reported, and the possibility of a ‘deep Köbner phenomenon’ has been entertained. Scarpa et al. [30] reported a case-control study examining the records of patients presenting with PsA and RA. In this study, 9% of PsA patients had a history of an acute event prior to the onset of arthritis compared with 1% of RA patients. While three patients had a history of an injury to a relevant joint, other acute events included recent surgery, therapeutic abortion, myocardial infarction, thrombophlebitis and phosphoric ester poisoning. In addition, Punzi et al. [31] found that 8% of patients with PsA compared with less than 2% of RA patients reported some form of trauma in the 3 months preceding the onset of their arthritis. These studies, which included a control group with RA and thus minimized recall bias, do suggest a potential association between trauma and the onset of PsA. Importantly, a significant history of trauma is only noted in a small minority of patients with PsA. Whether some of the clinical features of PsA in general may be a reflection of recurrent minor trauma, e.g. DIP joint involvement and plantar fasciitis, remains an intriguing possibility that may, in part, explain some of the clinical distribution of this condition. In addition, the fact that acute events as diverse as myocardial infarction, therapeutic abortion and poisoning were all found to predate the onset of PsA may suggest that the role of trauma is more related to psychologically stressful events rather than direct trauma to a joint. It is accepted that psychological stress can have a major impact on the severity of skin psoriasis, and it has been suggested that PsA occurs more frequently in patients with more extensive psoriasis. Psychological stress may therefore contribute to both the skin and the joint disease.

The psoriasis type itself may also have a role. Type 1 psoriasis occurs in patients under the age of 40 yr and appears to have a stronger genetic element in its aetiology. Rahman et al. [32] recently compared patients with PsA according to psoriasis type. Patients with type 1 psoriasis developed skin disease on average 9 yr prior to their arthritis. In contrast, those with type 2 psoriasis
developed skin and joint involvement within 12 months of each other. This may suggest different genetic and environmental susceptibility to PsA in these two groups. Alternatively it may simply reflect the fact that since inflammatory polyarthritis is more common with increasing age, the times of onset of the two conditions will appear closer in those with later-onset, type 2, psoriasis.

PsA remains an intriguing and poorly understood condition. Clinically, PsA remains difficult to define and it may be impossible at the clinical level to distinguish the co-occurrence of two common disorders that may modify each other from a distinct syndrome. In this setting, identification of a distinct aetiology would be extremely helpful. To date, immunogenetic studies have found few distinguishing factors. In contrast, there are several intriguing environmental clues. Large, well-designed and properly controlled studies should therefore be carried out to investigate the aetiology of this condition more thoroughly.

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References