HLA-B27

Chlamydia trachomatis in reactive arthritis

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Summary. Evidence of deposition of chlamydial antigen in the joint was sought in 10 patients (9 of them male) with classic sexually acquired reactive arthritis, 15 women with unclassified seronegative oligoarthritis involving the knee and 15 individuals with established rheumatic disorders not associated with genital-tract or other infections. Using a fluoresceinated monoclonal antibody to the major outer membrane protein of Chlamydia trachomatis (MicroTrak, Syva) in a direct immunofluorescence test, particulate antigen with physical characteristics of chlamydial elementary bodies was seen in synovial fluid cell smears or synovial biopsies, or both, from 6, 5, and 0 patients, respectively. No typical chlamydial intracellular inclusions were seen. Corroborative evidence of recent chlamydial infection was provided by the finding of high titres of serum chlamydial antibody in all antigen-positive patients with sexually acquired reactive arthritis, including 3 from whom a genital-tract isolate was obtained, and 3 of the 5 women with unclassified arthritis. It is postulated that Chlamydia trachomatis organisms reach the joint during acute genital-tract infection, and the processing and presentation by class I major histocompatibility determinants of chlamydial antigens is a critical step in the initiation of reactive arthritis in some patients.

Key words: Reactive arthritis – Chlamydia trachomatis – Reiter’s syndrome

Introduction

The discovery of the strong association between HLA antigens and certain major rheumatic disorders has firmly pointed to the involvement of microorganisms or other external environmental agents in the initiation and pathogenesis of such disorders as rheumatoid disease and forms of seronegative arthritis. Of these, reactive arthritis presents the clearest opportunity for understanding the relationships between such microorganisms and HLA as, in this condition alone, both a strong link with an HLA antigen, the class I determinant HLA-B27, and clearly identifiable precipitating infections exist. The term ‘reactive’ is used to describe arthritis which is associated with clear evidence of infection at a distant site but in which viable microorganisms are not found within the joint. It follows, therefore, that synovitis and perhaps other lesions are caused by mediators which are either formed at or released from the site of infection and which travel via the circulation to be deposited within the target tissue. Such mediators may be immunocompetent cells, antibody, immune complexes, toxins, or elements of the infectious agent itself. Reactive arthritis commonly follows bacterial diarrhea and sexually transmitted genital-tract infection though it is possible that infection at other sites may also be important in some instances. In approximately one-third of patients the features of Reiter’s syndrome are present.

In excess of 60% of individuals with Reiter’s syndrome and reactive arthritis possess the HLA-B27 antigen compared with approximately 7% of the healthy control population [1, 2]. Several Gram-negative bacteria have now been firmly implicated in the development of reactive arthritis with this complication developing in 1%-3% of individuals with Shigella flexneri, Salmonella enteritidis, S. typhimurium and Campylobacter jejuni infections. Infections by Yersinia enterocolitica and Y. pseudotuberculosis appear to be associated with a considerably higher incidence of reactive arthritis [2].
In the United Kingdom sexually acquired genital-tract infection is the most commonly recognised precipitator of reactive arthritis and this condition has been referred to as sexually acquired reactive arthritis (SARA) [3]. SARA is widely perceived as a disease predominantly of men, being infrequently diagnosed in women. However, unexplained seronegative arthritis affecting lower limb joints, often associated with HLA-B27, occurs not infrequently in females in the absence of clinical evidence of any precipitating infection and it is possible that in some of these cases arthritis is "reactive" to an undetected genital-tract infection.

Although several sexually transmitted microorganisms have been implicated as possible triggers for sexually acquired reactive arthritis, considerable attention has been paid to Chlamydia trachomatis. This microorganism is recognised as the cause of approximately 50% of non-gonococcal genital-tract infection [4] and is the cause of lymphogranuloma venereum, which is complicated by arthritis in approximately 5% of cases. Moreover, attention has been drawn to the similarities between human reactive arthritis and an arthritic syndrome in sheep and calves which results from systemic infection by Chlamydia psittaci [5]. Early studies using a complement fixation test demonstrated the presence of antibodies to C. trachomatis in a minority of patients with Reiter’s syndrome and both Schachter et al. [6] and Dunlop et al. [1] reported chlamydial isolates from joint material from patients with Reiter’s syndrome. Controversy has surrounded these findings as one isolate was subsequently identified as C. psittaci and the London group withdrew their findings having identified a possible source of contamination. Furthermore, with the introduction of more sensitive cell culture techniques for the isolation of chlamydia the number of reports of joint isolates has dwindled to a handful of individual instances, the significance of which is uncertain.

It is now clear that acute C. trachomatis infection is present in 42%–69% of individuals at or immediately preceding the onset of SARA [8–11]. Although this prevalence is comparable with that of chlamydial infection in uncomplicated non-gonococcal urethritis, the arthritic patients are distinguished by enhanced specific antibody and cell-mediated immune responses to this microorganism. Furthermore, Ford et al. [12] and Sieper et al. [13] have shown that the in vitro proliferative responses of synovial fluid mononuclear cells exceeds that of peripheral blood cells, supporting the suggestion that there is a source of antigen present in the joint.

This study therefore set out to determine whether chlamydiae or antigenic chlamydial fragments could be detected in joint material from patients with SARA and other unexplained seronegative oligoarthritis. This paper summarises data previously published elsewhere [14, 15].

### Patients and methods

Ten patients (9 males) with classical SARA and 15 women with undifferentiated sero-negative oligoarthritis in whom clinical examination and appropriate investigation failed to indicate a recognised diagnosis were studied. In all cases at least one knee was involved. In all cases a clinical genital-tract examination was undertaken by a genito-urinary (GU) physician. A history of recent sexual contact with a new partner and evidence of urethritis or cervicitis was mandatory for inclusion in the first group (SARA) and completely normal clinical GU findings were essential for inclusion in the second (undifferentiated seronegative arthritis) group. Control material was obtained from 15 patients with well-established, mainly chronic rheumatic diseases not associated with urogenital abnormalities. All denied symptoms of genital-tract disease, though none underwent specific genital-tract examination. The age, disease duration and HLA-B27 status of the patients and controls are shown in Table 1.

In the patients, genital-tract smears were examined, after giemsa staining, for evidence of urogenital inflammation. Attempts to isolate C. trachomatis from the genital tract and synovial fluid were made by inoculating cycloheximide-treated McCoy cell monolayers and serum chlamydial antibody was measured using a standard microimmunofluorescence test. Synovial membrane biopsy specimens were obtained at arthroscopy carried out under local anaesthetic. Chlamydial antigen was sought (by an experienced observer) in cryostat sections of synovial membrane and in smears of synovial fluid centrifuge deposits using a fluorescein-conjugated monoclonal antibody to C. trachomatis (MicroTrak: Syva) in a direct immunofluorescence test [14, 15].

### Results

The findings in each of the two groups of patients and controls are summarised in Table 2.