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SEXUAL AND ENTERIC BACTERIAL INFECTIONS ELICITING REACTIVE ARTHRITIS

(A REVIEW)*

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In this review synonymous definitions of reactive arthritis are discussed first. Major clinical symptoms, their infectious etiology and epidemiology define post-dysenteric and post-venereal forms of reactive arthritis. Classical (smear, culture, biochemistry, antigen detection) and molecular (DNA and RNA detections) techniques are used in the routine microbial diagnosis that is retrospective in the majority of cases. In the pathomechanism of this disorder, HLA-B27 antigen positivity of patients is a frequent risk factor. Molecular mimicry between microbial and self-antigens, abnormal antigen presentation leading to incomplete CD8+ T lymphocyte activation might contribute to the persistence of microbial antigens that elicit clinical symptoms. Treatment is rarely successful with antimicrobial chemotherapy.

Keywords: reactive arthritis, SARA, HLA-B27, CD8+ T lymphocytes, *Chlamydia trachomatis*, *Yersinia enterocolitica*

Historical background

The occurrence of arthritis following urethral discharge or an acute diarrhea was already mentioned by Hippokrates [1]. Simultaneous occurrence of arthritis and urethritis was described by Alonso Lopez de Hinijos, a Mexican monk in 1578 [2], while arthritis, urethritis and conjunctivitis in the same patient were diagnosed first by Martiniere in 1664 [1] and Stohl in 1776 (AA). Exact scientific description was made

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as “oculo-urethro-synovial triad” or “treponema arthritidis” by Hans Reiter in 1916, what is now called “Reiter’s syndrome” [3]. Specification improved when microbial techniques allowed differentiation of septic from aseptic arthritis. Four cases exhibiting triad symptoms following a *Shigella dysenteriae* outbreak were published by Fiessinger and Leroy [4]. Next, gonococcal infections and in 1950 *Chlamydia trachomatis* infections were recognized as most closely associated with the triad [5]. Post-dysenteric or epidemic Reiter and post-venereal or endemic Reiter syndromes were defined in 1981 [6]. Observing aseptic arthritis after gut infection with *Yersinia enterocolitica*, Aho and coworkers proposed a new definition as “reactive arthritis, (ReA)” that replaced all other terms used previously [7]. In the case of post-venereal forms, “sexually acquired reactive arthritis (SARA)” has become widely accepted [8]. HLA-B27 positivity as a risk factor in patients with ReA after enteral infections was described in 1973 [9].

Definition

Reactive arthritis is defined as aseptic arthritis triggered by an infectious agent located outside the joint. Antigens or nucleic acids of some microbes might be present in the joints. In several patients no triggering agent could be found. All these depend on adequate microbial techniques and now they can be separated from septic arthritides (in which microbes replicate themselves in the synovial fluid). Persisting microbes in the joint (e.g. Lyme disease) also result in the latter form. In rare transient forms seen in HLA-DR4 antigen positive patients, chronic arthritis develops, but neither microbial antigens nor nucleic acids are found by molecular techniques [1].

Major clinical entities leading to reactive arthritis

Neisseria gonorrhoeae infection can be followed by ReA. Non-gonococcal urethritis (NGU) is generally manifested as a mild, non-purulent and painless discharge accompanying or occurring within one month before the onset of arthritis. It may be asymptomatic or accompanied by severe prostatitis. In women, cervicitis is common with vaginal discharge, but sometimes it has no symptoms. *Chlamydia trachomatis* is the most frequently isolated agent [1, 8]. The similar role of mycoplasmas and *Ureaplasma urealyticum* has not been clearly established [1, 10]. SARA develops in 1-3% of NGU patients, of which the majority is male. ReA following acute urogenital symptoms is relatively rare in females. Interestingly enough, sterile urethritis lasting for few days may be a part of post-dysenteric phenomenon [1, 11].

Intestinal symptoms as an acute diarrhea also accompany or within one month precede the onset of arthritis. One to three percents of such patients develop ReA. In general, dysenteric symptoms in these patients are milder than in non-arthritis patients. The incidence of this form of ReA is declining. It is most frequent in age group between 20 to 40 years, and the ratio of male and female subjects is 1:1. The most frequent triggering agents are *Yersinia enterocolitica* (rarely *Y. pseudotuberculosis*), *Salmonella enteritidis, typhimurium, abony*, *blockley, schwarzengrund, heidelberg, haifa, mania, newport, Clostridium difficile, Vibrio parahaemolyticus, Shigella flexneri* serotypes 1 and 2 and, *Campylobacter jejuni, coli, fetus*. *lari.* They disappear from the bowel when joint symptoms arise, except salmonellae [1].

Screening for microbes

Arthritis develops within 2–3 weeks post infection. Bacterial cultures of synovial fluid and tissues are negative. In the majority of clinical cases, microbial diagnosis is retrospective and based upon tests conducted at time of urogenital or intestinal infections [1, 8, 12]. Steadily increasing number of *Treponema pallidum* infections will bring into focus the syphilis associated ReA again. Seroconversion is proven by Venereal Disease Research Laboratory (VDRL) test, Treponema Pallidum Immobilization (TPI) or lately, by Western blot. As *Neisseria gonorrhoeae, Salmonella and Shigella* species can induce both infectious and reactive arthritides; therefore puncture of synovial cavity is unavoidable to set up exact diagnosis. Smear, cultivation, detection of DNA by polymerase (PCR) or ligase (LCR) chain reactions are the generally used diagnostic methods. In the majority of ReA cases, serovariants D-K of *Chlamydia trachomatis* infect the genitourinary tract, but joints are free of infectious microbes. HLA-B27 antigen positive subjects are more sensitive to chlamydial infection than negative individuals [1, 8, 12]. As exceptions, in few documented cases of ReA, *Chlamydia* could be cultivated from the synovial fluid [8] but their DNA and RNA can be detected regularly by molecular techniques [13, 14]. On the contrary, lipopolysaccharide endotoxin and the outer membrane polypeptide cannot be shown from the synovial fluid. These suggest again that no Chlamydia replication takes place in the joints, the microbes are latent. Their antigens may be detected by microimmunofluorescence with specific antisera on urethral or cervical scrapings, while DNA is shown by PCR or LCR. Gene probes are used to detect specific RNA. Antibody quantification has no significant predictive value for ReA. Antibiotic treatment has a beneficial effect if given at the very beginning of the onset of ReA symptoms [15].

Yersinia enterocolitica is the most frequent provocative agent of ReA in Northern Europe, especially in Belgium, where eating row pork may result in infection. No nucleic acids of it have been detected in the synovial fluid, but polypeptide antigens could be shown [16]. No antibiotic treatment of humans and experimental animals is effective during the course of ReA induced by *Yersinia*, but high dose fluoroquinolones might prevent the onset of ReA symptoms if given in the early phase of gut infection [17–19]. These raise the possibility that *Chlamydia* and *Yersinia* induce ReA in different ways [12]. Stool cultures on selective media, carbohydrate fermentation, biochemical reactions, phage-, bio- and colicin typing, agglutination with specific antisera are the major methods of practical importance to identify *Y. enterocolitica, Salmonella* and *Shigella* species, *Vibrio parahaemolyticus* as well. Anaerobic cultivation, detection of A and B exotoxins by neutralization in cell culture, ELISA are used to identify *Clostridium difficile*. *Y. pseudotuberculosis* can be shown in skin biopsy specimen or agglutination is used to quantitate antibodies. Diagnosis of *Campylobacter* species is complemented by dark field microscopy, selective cultivation, oxidase test, and serotyping O and H antigens. Rarely, another microbes also might induce ReA. Hepatitis B is transmitted sexually or by intravenous drug abuse. Screening both antibodies and antigens is carried out by commercial ELISA kits. Herpes simplex virus types 1 and 2 infections are diagnosed by PCR, LCR or cultivation followed by verification through immunofluorescence or molecular methods. So far no ReA has been detected following natural infection with *Shigella sonnei, S. typhi, E. coli* infections or microbes inducing chronic enteritis [1].

Newly recognized forms of ReA might complicate the picture. Arthritis-dermatitis syndrome occurs in 8 to 36 percent of patients (mostly females) after jejunocolonic bypass surgery in the first three postoperative years [20]. The syndrome is associated with elevated levels of circulating immune complexes to *Escherichia coli, Bacillus fragilis* or group D *Streptococcus*.

Whipple's disease is a rare disorder with polyarthritis, which appears to subside several months to 2 years before the onset of diarrhea. Applying PCR, a previously uncultured new bacterium, *Tropheryma whippeli* was discovered as the possible causative agent, that has some homology with the actinomycetes [21].

Pathogenic considerations

The inflammatory nature of ReA is proven by an elevated erythrocyte sedimentation rate, an increased concentration of C-reactive protein. The synovial fluid contains more than 2000 cell/mm^3, with a majority of polymorphonuclear leukocytes. Its complement concentration is normal. Periarticular tissues show vascular congestion

and perivascular cell infiltration, mainly with neutrophils. Other histological findings resemble psoriasis [1, 8, 10, 13]. The close but not exclusive association of ReA with HLA-B27 antigen suggests several possible roles as an antigen of MHC class I molecule. In HLA-B27 positive patients, upregulated mechanism of neutrophils might augment inflammatory response [22]. HLA-B27 molecule presents specific peptides to T helper cells, which are recognized as autoantigens by cytotoxic T cells, but antigen presentation seems to be inefficient in ReA patients [12, 23]. HLA-B27 molecule might behave as a receptor by binding bacterial antigens then this complex induces an abnormal immune response [12, 24]. It is also plausible that the amino acid sequence of HLA-B27 peptide and that of certain bacteria have high homology. The human immune system recognizes bacterial components as self – and consequently autoimmune reactions damage the synovium. Partial homology between HLA-B27 antigen and *Yersinia* and *Treponema* species has already been detected [12]. Molecular mimicry between the presented enterobacterial oligopeptide on antigen presenting cells and self-antigens was also shown [12]. Microbes possess thousands of antigens, but those that induce ReA are regarded as dominant antigens. These might be expressed or accumulated in the special microenvironment of the joints. The synovial fluid is acidic and lacks oxygen, consequently favors expression of heat shock proteins (hsp) and cationic polypeptides, which preferably bind HLA-B27 molecules. Some microbial antigens playing a role in the pathogenesis of ReA have already been identified: e.g. hsp57, a 30 kDa protein and a 18 kDa histone-like cationic polypeptide in *C. trachomatis*, and a 61 kDa hsp, a 23 kDa ribosomal and a 19 kDa urease polypeptide in *Y. enterocolitica* [12]. *In vivo* experiments support biochemical data: in HLA-B27 transgenic rats ReA does develop in the presence of normal intestinal flora, but does not in germ-free-animals [26].

Studies on *Yersinia* induced Reiter' syndrome demonstrated low-level initial IgM production with strong IgG and especially IgA response. Several antigenic determinants elicit antibody response with consequent immune complex formation in the serum and synovial fluid. T lymphocytes are activated locally in the joints by antigens: their synovial clonal expansion upon stimulation with antigens of *Chlamydia* and *Yersinia* is stronger than that in the blood. In addition to activated CD45RO+ T cells, large amounts of CD45RA+ resting cells are found in the synovial fluid. The majority of T cells are CD4+ although they are not antigen specific. Oligoclonal CD8+ cells present in the synovium might have the major role in the pathomechanism of ReA through cytotoxic activity. *C. trachomatis* is an obligatory, while yersiniae and salmonellae are facultative intracellular parasites. It has been shown that macrophages carrying these bacteria induce a weak CD8+ cytotoxic response. The synovial fluid of ReA patients contains high level IL-4 (Th2 type) [27]. All these phenomena might

suggest an incomplete elimination of triggering microbes and their persisting antigens in the joints induce inflammation [10, 12–14, 28].

Microbial differential diagnosis

If gonococcus infection is suspected (usually in women), culture of blood and synovial fluid must be made concurrently. Upon therapeutic intervention the infectious form of arthritis subsides dramatically within few days. HIV infection induces acute but transitory joint pains. Concomitant ReA may be worsened by HIV. Therefore the search for HIV seroconversion is recommended in even typical cases of ReA. In parvovirus arthropaties detection of viral DNA in the serum, lymphocytes, tissues by PCR and IgM/IgG detection by serological tests clarifies origin. Lyme disease is confirmed microbially after detecting IgG/IgM (ELISA, immunofluorescence, Western-blot) or cultivation of *Borrelia burgdorferi*. High dose penicillin treatment promptly relieves symptoms in Lyme disease but is ineffective in real ReA. Beta-hemolytic streptococci cause rheumatic fever. Intravesical injection of bacillus Calmette-Guérin in patients with bladder tumor may induce arthritis. Occasionally brucellae, *Mycobacterium phlei* or parasitic infections are associated with arthritis, but these are cured by a specific treatment, which is not in case of ReA [1, 10, 13].

Antimicrobial treatment

There is no antimicrobial cure for the majority of ReA cases due to retrospective diagnosis. But *C. trachomatis* frequently remains present in patients with urethritis or cervicitis. Combination of trimethoprim and sulfamethoxazole, furthermore tetracycline or ciprofloxacin treatments for 3 months eradicate this microbe with beneficial clinical effects regarding ReA. The number of patients with SARA has significantly decreased in the recent years due to the early treatment of non-gonococcal urethritis. Immunosuppressive therapy may reduce clinical symptoms, but should be avoided in young adults [1, 8].

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