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Reactive arthritis

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Abstract

Reactive arthritis (ReA) frequently is a sequel of gastrointestinal or genitourinary tract infections, previously identified as developing sterile inflammatory arthritis. When the pathogenesis of ReA is considered the most definite evidence on the role of microbial agents is based on the demonstration of microbial agents in the synovial fluid. Presence of wide range of difference in forms of immunological and clinical responses is depend on individual responses. Biochemical reactions of the cellular level, reflecting addition of host-microorganism relationship are recent advances in understanding ReA. Patients are usually young adults, the average age-range is between 30-40 years. The most obvious involvement of the disease is in the joints. Joint involvement can create aclinical spectrum from arthralgia to severe polyarthritis.

Keywords: Reactive arthritis, arthritis, Chlamydia

Description

Reactive arthritis (ReA) may be defined as a sterile inflammatory arthritis, commonly developing as a sequel to previous infection of the gastrointestinal or genitourinary tract. The term, ReA, was first suggested in 1969 [1]. In 1974, Aho et al. [2] theoretically reported that onset of infection and subsequent aseptic arthritis were associated and described the condition as arthritis developing during or right after the infection in another part of the body but where the microorganism had not entered the articular cavity. Thereafter, studies have demonstrated that the antigens of the trigger microbes could be revealed in the affected synovial fluid and synovial tissue. Replication of these microorganisms was rarely shown in the joints of patients with typical characteristics of ReA [3-5].

The term, arthritis secondary to Chlamydia, was used to define reactive arthritis, specifically caused by a Chlamydia infection [6]. Post-streptococcal ReA is used to describe arthritis, exhibiting similar features to streptococcal throat infection-related ReA. However, potential for causality has not been confirmed yet [7,8].

There are no criteria for classification and diagnosis of ReA, which are proved to be valid. Following a few reactive arthritis classification study, according to the classification proposed by Pacheco-Tena for clinical and experimental studies, ReA has been investigated in three categories namely probable, definite, and undifferentiated [9].

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Epidemiology

Community-based studies are currently going on to estimate the incidence of ReA. The total incidence is estimated to be 0.6-27/100.000 in these studies. In a study performed in Finland in 1978, the annual incidence of ReA following intestinal infections and genitourinary infections was detected to be 27/100,000 while in another study in 2000, it was 10/100,000 [11-12]. A Norwegian study reported the incidence of ReA following enteric infections to be 5/100,000 and 5/100.000 following urogenital infections with the total annual incidence being reported as 10/100,000 [13]. In a 2002 study in Sweden, the incidence of ReA following enteric infections and following urogenital infections was reported to be 18/100,000 and 1/100,000, respectively [14].

In a USA study, the estimated incidence of ReA was found to be 0.6-3.1 cases/100,000 [15]. Another study in Czech Republic reported the age-standardized incidence to be 9.3/100,000 [16].

Trigger Infections

The primary focus of the infection is usually the mucosal membrane of the intestines or the urogenital tract. Classical microorganisms of the GIS tract include *Yersinia*, *Salmonella*, *Shigella*, and *Campylobacter*. In the recent years, epidemiologic studies in Denmark reported arthralgia in a considerable number of patients and arthritis in some cases along with gastrointestinal infections caused by diarrheagenic strains of *Escherichia coli (E.coli)*. In clinical series, E. coli was associated with ReA. Case-based studies have demonstrated that *clostridium difficile (cl.difficile*) was associated with ReA [17,18].

Chlamydia trachomatis (C.trachomatis) is the most common cause of cases of ReA secondary to genital infections. *Ureoplasma urealiticum (U.urealiticum)* has been associated with ReA; however, mycoplasma genitalium is another microbe related to urethritis and whether it is an independent ReA trigger in the absence of chlamydial infection has not been elucidated clearly[19,20]. Several studies have indicated that *Neisseria gonorrhea* was a cause of ReA and other inflammatory arthritis, however, the nature of this association is not known yet [21,22]. *C. trachomatis*, a respiratory pathogen, can be found in 10% of the patients with ReA [23]. Beta hemolytic streptococcus, another one of the respiratory infectious pathogens, is a conventional trigger of acute rheumatic fever. ReA has also been described as a sequel of streptococcal throat infection [24]. Percentage rates of ReA secondary to different pathogens are presented in Table 2.

Table 1. Primary classification for ReA (modified by Braun et al. in 2000 (10))

Major criteria	1-Arthritis, co-existence of two or three of the following criteria: asymmetric mono- or oligoarticular dominantly, lower extremities 2- Primary symptomatic infection: together with one or two subsequent findings -enteritis (diarrhea for at least one day, up to 3 days to 6 weeks of arthritis onset) -urethritis (dysuria or discharge for at least one day (up to 3 days to 6 weeks of arthritis onset)
Minor criteria	At least one of the following criteria: 1-Evidence for triggering infection - Positive amplification test for chlamydia in the morning urine or urethral/cervical swab - Positive stool culture for Rea-associated enteric bacteria - Evidence for persistent synovial infection (positive immunohistology or PCR for chlamydia) **Definition of reactive arthritis:** Defined ReA; two major criteria and one minor criterion Probable ReA; two major criteria, no minor criteria or one major and one minor criterion Exclusion criteria Lack of another cause to explain arthritis

Table 2. Development of ReA following breakouts of Campylobacter, Shigella and Yersinia

Bacteria	Number of patients affected by breakout	ReA,%	HLA-B27 frequency	Reference
C. jejuni	347	0.7	0/1	Eastmont(25)
C. jejuni	106	1.8	1/1	Bremell et al. (26)
Shigella	602	1.5	NA	Noer(27)
S. sonnei	184	0	-	Simon et al. (28)
S. flexneri 2a	636	1.5	2/3	Simon et al. (28)
S. flexneri 1b	709	1.5	3/3	Simon et al. (28)
S. flexneri 2a	205	2.3-6.9	-	Finch et al. (29)
Y. enterocolitica	117	0	-	Lindholm & Visakorpi (30)
Y. pseudotuberculosis	NA	3	1/1	Tertti et al.(31)
Y. pseudotuberculosis	NA	21	¾	Tertti et al.(32)
Y. pseudotuberculosis	38	12	3/3	Hannu et al.(33)

Etiology and Pathogenesis

Many interventions have been made to regulate the classification for ReA [9,10-41]. Etiologic classification is one of the methods, which is mostly studied. This has led to conduct of studies to investigate the association between specific pathogens and ReA. While the organism itself could not be shown in the joint directly in these studies, the immune response related to the effective pathogen could be shown by serologic or cellular response.

Most direct evidence on the role of microbial agents is based on demonstration of microbial agents in the joint fluid. Most direct evidence on persistent agents in the joint fluid is related to *Chlamydia*. Many investigators have shown the DNA and RNA particles in the joint fluid of patients with Chlamydia-associated ReA. An experimental model showed that Chlamydia phagocytosed by synovitis could induce chronic aseptic arthritis and synovitis could serve as a reservoir even after a long time following the culture of this agent for this microbial agent [42]. There is some evidence showing that these persistent organisms are metabolically changed in the joint and could progress to a stationary phase that could render them more resistant to antibiotics. These characteristics have also been shown for *Chlamydia pneumonia (C.pneumonia)* with similar characteristics to those of C. trachomatis with respect to viability and metabolic activity. However, compared to that of C. trachomatis, the DNA of C. pneumonia showed a lower incidence in the synovial tissues [43]. However, the significance of these findings

for etiopathogenesis of joint disease is still controversial [44]. In synovium of certain asymptomatic patients, chlamydial nucleic acids were detected. Still, in some patients with chronic arthritis, publications from Latin America, England and the USA have shown bacterial DNA and RNAs of a wide spectrum also including bacteria, which have not been previously associated with ReA [45- 47].

There are major individual differences with respect to post-infection clinical and immunologic responses. However, there are advances in perception of the biochemical events, reflecting the host-microorganism relationship at a cellular level. Bacterial binding and invasion, interaction between bacterial invasion proteins, and surface receptors of target host occur. If foreign antigens show a cross reaction with normal host tissue after infection, they may initiate an autoimmune attack against joint structures. A similar cross-reaction has been shown between the streptococcal M protein and cardiac myosin and in this respect, acute rheumatic fever represents an example for the theories of microbial pathogenesis [48]. Common presence of similarity between the core proteins of the host and microbial protein sequences is apparent and there may be some impairment in binding of the peptides to receptors on the T cell and MHC on the antigen-presenting cells. Infection may be providing stimuli to the self-antigens, which could impair immune tolerance, also via mechanisms other than molecular mimicry. Tissue necrosis and local cell necrosis may be revealing the hidden epitopes of the self-antigens. Through this mechanism, silent auto-reactive T cells may be activated [49]. Inappropriate activation may occur secondary to upregulation of the co-stimulator molecules on the antigen-presenting cells and the MHC molecules.

While the route used by many organisms to enter the joints has not been elucidated yet, data suggest that leukocytes embodying these pathogens could exhibit alternative carrier patterns [50]. There are opinions suggesting that the mechanisms of the organism to phagocyte or start intracellular killing, involved in pathogen killing, may be impaired. Chlamydia heat shock proteins stop activity, particularly above hsp60 and recent studies have described three expressions of the gene encoding *C. trachomatis* hsp60, which may be different in case of active or persistent infection [51].

A study performed in 11 ReA patients showed that mononuclear cell stimulation in the synovial tissues caused a low level of IFN-gamma and TNF-alpha but a high level of IL-10 release [52]. When human synoviocytes are infected with *C. trachomatis* in vitro, IL-6, TGF-beta, GM-CSF production occurs [53]. In a study in patients with ReA, induced by chlamydia, HLA-B27 positive patients were observed to have a lower level of IFN-gamma in their synovial fluid and these patients had a more chronic course [54]. This data suggests that reduced IFN-gamma production could be responsible for persistence of arthritis.

The strong correlation between HLA-B27 and spondyloarthritis (SpA) indicates the role of antigen-specific MHC class 1-limited CDS CTLs in this disease via indirect route. One should know that the CD8 T cells in the synovial fluid could express the NK (natural killer) receptor [55].

Clinical Course

It usually takes 1-2 weeks from onset of infection to onset of musculoskeletal symptoms; this interval may extend to 4 weeks in case of chlamydia infections. Trigger infection may be asymptomatic, which makes it more difficult to diagnose. ReA patients are usually young adults with a mean age of 30-40 years. The disease is not common among children [35,56,57] (). While ReA triggered by *C. trachomatis* is diagnosed more commonly in males, ReA induced by gastrointestinal infections exhibits a similar risk between females and males. Other than the musculoskeletal system findings of the disease, findings of cutaneous and mucous membranes, the urogenital system, ocular, and renal findings may also be observed in the clinical course.

Musculoskeletal system: The most marked involvement occurs in the joints. Joint involvement may form a clinical spectrum from arthralgia to polyarthritis. It usually manifests as asymmetrical mono-oligoarthritis involving the knee and the ankles. Sausage digit (dactylitis) is the extra-synovial swelling, occurring in the whole finger due to the enthesophatic quality of the disease. Enthesophatic lesions most commonly involve the Achilles tendon-plantar fascia.

Cutaneous and mucous membranes: *Keratoderma blennorrhagica* are hyperkeratotic lesions that occur particularly on the soles of the feet, palms and fingers and look very similar to pustular psoriasis. The presence of these lesions indicates that course of the disease will be more severe. Circinate balanitis is a pain-free, erythematous, well-bordered lesion that occurs on the glans and corpus of the penis. Similar lesions may also be observed in the mouth, on the soft and hard palate mucosa, gingiva and tongue. Hyperkeratosis and parakeratosis may occur on the nails that are similar to that observed in psoriasis.

Gastrointestinal system: Diarrhea may be observed one month or within a shorter duration before the onset of musculoskeletal symptoms; however, it may remain unnoticed since its course is very mild in most patients.

Urogenital system: Urologic symptoms, ranging between non-specific urethritis and acute hemorrhagic cystitis may occur prior to onset of arthritis, with concomitant orchitis, epididymitis, and prostatitis. Cervicitis occurring in females may manifest with a potentially unnoticed course involving mild vaginal discharge.

Ocular Findings: Conjunctivitis, a part of the classical triad, may occur prior to or during arthritis. Discharge in conjunctivitis, which may be lateral or bilateral, is sterile,

and it may disappear in a short while or may also lead to complications including episcleritis, keratitis, and even corneal ulceration. Acute anterior uveitis is another ocular manifestation, which commonly occurs and potentially recurs. Ocular lesions may be the exclusive clinical finding of ReA. One should keep in mind that 1/3-1/2 of the patients with acute uveitis have a rheumatologic problem [58].

Renal Findings: Half of the patients may have mild renal findings such as proteinuria, microhematuria and aseptic pyuria. Glomerulonephritis and IgA nephropathy are pathologies that occur very rarely and usually do not impair renal functions.

ReA may exhibit variable manifestations, including self-limiting minor arthropathy, spinal rigidity, loss of vison, cardiac involvement, or a catastrophic clinical course which may result even in death.

Late sequels secondary to ReA may occur during the clinical course. These include in order: spinal (sacroiliitis, non-marginal, asymmetrical syndesmophyte), ocular (anophthalmia, blindness), CVD (cardıovascular disease): (conduction disturbances, palpitations, murmur, aortic failure), CNS: (peripheral neuropathy, hemiplegia, cranial nerve involvement), pulmonary: (pleuritic, pneumonia, pleuritic chest pain) and at a lower rate: purpura, thrombophlebitis, amyloidosis.

Laboratory findings

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may increase during the acute period. Mild leukocytosis and anemia may be observed. Routine urinary investigation may reveal aseptic pyuria. Synovial fluid investigations may show some increase in cells together with neutrophil abundance. No growth in culture may occur and the level complement is usually normal. Synovial biopsy reveals non-specific inflammation findings. ECG (electrocardiography) should be performed in ReA patients to investigate the potential for cardiac involvement.

In addition to the clinical course, the diagnosis of ReA is also based on the diagnosis of the trigger infection. Isolation of the enteric infection from the stool during the acute phase is usually possible. However, patients may have recovered before onset of arthritis complications upon occurrence of arthritic complications and the bacteria may not be revealed in the feces. Therefore, the laboratory diagnosis of ReA is commonly based on detection of the specific antibodies in the serum.

Salmonella and Yersinia infections are associated with the strong antibody response and thus detection of the specific antibodies against these microbes is used in the clinical series. There are no reliable serologic methods in case of gastrointestinal infections such as Shigella.

Yersinia specific IgA antibodies and Salmonella specific IgM, IgA and IgG antibodies can be detected for months or years in the sera of patients with ReA [59,60]. In acute ReA, induced by Yersinia, Ig A and Ig G antibodies can be detected at nearly 100% and IgA can still be detected at 84% after a year [89]. In case of Salmonella infection, the sensitivity of showing the IgM class antibody with EIA (enzyme ımmunoassay), and Widal agglutination is 92% and 64%, respectively [61]. 2-5 months after the onset of infection, approximately 94% of the patients still give a positive reaction with EIA while Widal agglutination is positive in only 14% of the patients.

For diagnosis of *C. trachomatis*, nucleic acid amplification tests, which are superior tests, are used to investigate bacteria in the first portion of the morning urine [62]. These tests are practical for patients and the results can be compared to those obtained in the urogenital swabs. Additionally, various tests including complement fixation, micro-immunofluorescence (MIF) and enzyme immunoassay from the serum samples are used; however, these tests are not beneficial in lower urinary tract infections because these infections do not induce an adequate antibody response. The other limitations of these tests include the failure to differentiate serologic cross-reactions between *C. trachomatis* and *C. pneumonia* and its blocking effect on differentiation between previous or current infections for persistent antibodies [62]. Additionally, the relatively high prevalence of the positive antibodies in the normal population limits the use of these tests for diagnosis of *C. trachomatis* infection. Positive result for chlamydia in the joint with PCR is very valuable for diagnosis; however, current methods are for investigation of Chlamydia in the urine and they are not validated for diagnostic use in the synovial sample. MIF is still the recommended serologic method for diagnosis of acute C. pneumoniae. MIF is inadequate in determining IgG antibodies; however, it can detect IgM and IgA antibodies. Based on current reviews, positive serology alone without urinary tract infection anamnesis is not enough in diagnosing ReA induced by Chlamydia [63].

Other rheumatic conditions such as Lyme arthritis, rheumatoid arthritis, viral arthritis and osteoarthritis should be ruled out based on the clinical course and relevant tests.

Approximately 90% of AS patients have HLA-B27 antigen. In some of the previous studies investigating this association in ReA patients reported a quite high rate for this antigen (nearly 60-80%). In epidemic studies or epidemiologic surveys (at the level of population), the HLA-B27 frequency has increased very little or had not increased at all [64]. However, one should also note that the presence of HLA-B27 may be associated with a more severe arthritis and could lead to a long-term disease [65-67].

Treatment

Treatment of the trigger infection

All patients with acute *C. trachomatis* infection should be treated with azithromycin (1 gram as a single dose) or doxycycline (200 mg/day for a 7-day period). Generally, gastrointestinal infections associated with ReA are self-

limiting and should not be treated with antimicrobial agents. While there are no controlled studies, there are some data showing that initiation of antibiotic treatment during the early phase of infection could prevent recurrent ReA development [68]. If campylobacter is suspected, acute enteritis should be treated with fluoroquinolone or macrolides, and azithromycin or macrolide should be used in acute urethritis. For *C. pneumoniae* infection, erythromycin and tetracycline are commonly used; new macrolides such as ketolides and fluoroquinolones are the other potentially effective drugs.

Treatment of acute arthritis

Use of high-dose and long-half-life non-steroidal anti-inflammatory drugs is usually very beneficial. If the patient has mono- or oligoarticular disease, intra-articular CS (corticosteroid) injection may be used. Enthesopathy also responds to local CS injection. Use of systemic CS is indicated in patients with severe polyarthritis. The initial dose of prednisone/prednisolone is usually 20-40 mg/day.

Antimicrobial treatment in acute arthritis

There are a few studies reporting the effects of antibiotics in acute ReA. Excluding a placebo-controlled study in patients with early ReA [69], all other controlled studies on antibiotic treatment in ongoing ReA showed that they were not effective on the disease process. Only in a study with positive results, three months of treatment with lymecycline highly reduced the ReA process in patients with ReA associated with *C. trachomatis* [70].

In a cohort on salmonella outbreak, two studies on early antibiotic treatment were assessed [71,57]. None of these studies demonstrated the efficacy of early antibiotic treatment in preventing ReA. There is no evidence showing that short-term antibiotic treatment prevents ReA associated with *C. jejuni* or *Campylobacter coli* [72]. There are a few studies on *Yersinia spp*. In a study, antimicrobial treatment consisting of trimethoprim, doxycycline or ciprofloxacin eliminated *Y. enterocolitica* from the intestines of patients with ReA; however, its effect on the course of arthritis is not known [73]. Considering all this data, antimicrobial treatment is not recommended except ReA secondary to chlamydia infections.

Disease Modifying Drugs (DMARDs)

Since the short term results of ReA are favorable, nearly half of the patients improve within the first month. The mostly emphasized drug among DMARDs is sulfasalazine (SLZ). If initiated within the first 3 months of ReA, it was shown to induce remission more rapidly than that in the placebo-receiving group [74]. There are studies showing that SLZ is effective when used in chronic ReA [75].

Biologic agents

Although tumor necrosis factor-blocking (TNF) agents have proven their success in treatment of AS and undifferentiated SpA, there are no large or controlled studies on the use of biologics in treatment of ReA. The efficacy and safety of etanercept (25 mg subcutaneous) was evaluated in a 6-month open-ended study in 16 patients with undifferentiated SpA or ReA; 9 of 10 patients, who completed the treatment, responded well to treatment [76].

Case reports of biologics, used in the treatment of ReA, were obtained mostly from studies on infliximab. Results of these published cases are considered favorable. However, there are also cases of patients with refractory plantar fasciitis or refractory Achilles tendonitis [77]. Due to the fact that microorganisms may persist, there are certain author opinions on inappropriateness of using TNF alpha blocker agents in patients with ReA, induced by chronic Chlamydia [78].

A recent study reported that the combination of doxycycline and rifampin significantly improved the symptoms of chronic SpA compared to doxycycline treatment alone [79] and patients receiving azithromycin and rifampin combination achieved a more effective remission [80].

Prognosis

The mean duration of acute ReA is 3 to 5 months. If arthritis lasts more than 6 months clinically, development of chronicity should also be considered. Two studies evaluated the long-term prognosis of ReA, induced by Salmonella [67]. In an American study with 5-year follow-up, 1/3 of the patients completely recovered and half of the patients developed chronic arthritis during follow-up. 2/3 of the patients continued having subjective complaints. In the other study, patients were followed for a mean of 11 years and 16% of the patients were observed to have a chronic course. In this Finnish study, many patients were observed to have late symptoms, which were only transient subjective findings without objective ones. A few patients developed sacroiliitis; this could be explained by the fact that 88% of the patients in the study were HLA –B27 (+).

A study reported on the long-term results of ReA, induced by Shigella. In a Finland study investigating patients, who had Shigella arthritis 20 years ago, sacroiliitis was detected with AS as 14% and 32% radiologically [81]. There are a few studies on the long-term prognosis of ReA, induced by Y. enterocolitis [82]. In these studies, the longest mean follow-up was 10 years. 25% of the patients developed sacroiliitis radiologically; most had HLA-B27 antigen. Even if similar findings were associated with Y. pseudotuberculosis-associated ReA, findings were present only in 4 patients. The evidence on the long-term prognosis of ReA, induced by Campylobacter, is inadequate with only one patient reported [83].

The long-term prognosis of ReA, triggered by *C. trachomatis*, is not known. Chronicity was reported at a high rate in patients with severe ReA, induced by non-gonococcal urogenital pathogens, where *C. trachomatis* was not a requirement. In the Finnish-Danish study, chronic joint symptoms and chronic lumbago was reported at 68% and 41%, respectively. In the study, the

presence of HLA-B27 was strongly correlated with chronic lumbago and sacroiliitis. During the 10-year follow-up, radiologic sacroiliitis was observed in 30% of the patients with ReA, triggered by urethritis. There was no study to evaluate the long-term prognosis of ReA, triggered by *C. pneumonia* [84, 85]. In addition Sert et al . in a study of Toxoplasma gondii have shown it may cause reactive arthritis [86].

The factors determining the progression of acute ReA to SpA are not clearly known; however, the type of infection, presence of HLA-B27, positive family history for AS or SpA and presence of chronic intestinal inflammation are known factors [87].

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