

Update on the diagnosis and management of Reactive arthritis (Reiter's syndrome)

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ABSTRACT

The reactive arthritis (Reiter's syndrome) is an asymmetric, non septic inflammation of several joints, mainly of the lower limbs, associated with the occurrence of a change called "enthesitis" (inflammation of the tendon), and proceeded by an extraarticular manifestation and by infection of various microorganisms. Classically it includes the triad arthritis, urethritis, and conjunctivitis. Approximately 80% of patients are positive for the histocompatibility antigen called human leukocyte antigen (HLA)-B27; therefore, reactive arthritis is strongly associated with HLA-B27. The disease is classified as type of seronegative spondyloarthropathy. For most patients, symptoms will go away in 2-6 months. Reactive arthritis can affect the heels, toes, fingers, low back, and joints, especially of the knees or ankles. The infection that causes reactive arthritis usually presents as diarrhoea or as a sexually transmitted disease. Diagnosis of reactive arthritis is difficult due to vast variation of the clinical features, largely empiric, relapsing courses and classical triad. Systemic treatment of reactive arthritis can be done with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying agents, immunosuppressive therapy, biological agents and antibiotics. Reactive arthritis can also be managed by nutrient supplements and herbal agents. The present review discusses various aspects of reactive arthritis disease, which helps for the future investigations of diagnose and management.

Keywords: Reactive arthritis, Reiter's syndrome, Rheumatoid arthritis, inflammation, and cytokines.

INTRODUCTION

Reactive arthritis is an autoimmune and inflammatory disease, considered as arthritis group of disease. Rheumatoid arthritis (RA) is an autoimmune and a symmetrical polyarticular disease of unknown etiology that affects primarily the diarthrodial joints, which is characterized by chronic inflammation of the synovial joints [1]. The acute inflammatory response consists of three main vascular effects: vasodilatation and increased blood flow, increased vascular permeability, and leukocytosis into the injured tissues [2]. These pathological aspects give the link between RA and reactive arthritis. Reactive arthritis belongs to a group of diseases known as autoimmune seronegative spondyloarthropathy that is associated with a high incidence of human leukocyte antigen B 27 (HLA B27). Reactive arthritis is a disease with diverse clinical manifestations affecting the peripheral joints, spine, skin, eyes, digestive and other systems. The variety of symptoms means that patients, especially in the initial stage of the disease, are treated by the specialists of other fields than rheumatology. The spondyloarthropathies also called as triad of arthritis, urethritis, and uveitis [3, 4]. It has been postulated that bacterial antigens persist within the synovium and other tissues, stimulating a proliferative T-cell response. This proliferative T-cell response eventually targets autoantigens, causing inflammation and tissue destruction. After a latent period of one week to one month, ocular symptoms develop, such as sterile conjunctivitis or iritis, combined with oligoarthritis. The oligoarthritis is usually asymmetric and affects the lower extremities, including the knees or ankles. Enthesopathy (inflammation of tendons) at their insertions, especially the Achilles tendon, and dactylitis, or sausage digits, also may occur.

Constitutional symptoms, such as fever and weight loss, are not uncommon during the acute phase of reactive arthritis [5].

Reactive arthritis to Reiter's syndrome

Conjunctivitis, urethritis and arthritis emerging after the prior onset of diarrhoea were first described by Stoll in 1776. In 1818, Benjamin Brodie described five cases of conjunctivitis, urethritis and arthritis with a history of venereal diseases. In 1916, Fiessinger and Leroy described four patients with an oculo-urethro-synovial syndrome following diarrhoea caused by *Shigella*. In the same year, Hans Reiter (a German army doctor) described a triad of symptoms: nongonococcal urethritis, conjunctivitis and arthritis suffered by a young officer with bloody diarrhoea and linked these symptoms to the *Treponema* infection, at this situation no name for this type of condition, he decided to call it Reiter's syndrome. Until modern times, many researchers used the term Reiter's syndrome for this triad of symptoms. In 1969, the use of the term reactive arthritis was proposed, and in 1977, following the disclosure of the war crimes committed by Hans Reiter, it was recommended not to use the name of Reiter's syndrome due to ethical reasons. Based on the analysis of the literature the proportion of authors who use Reiter's name to describe the syndrome has decreased from 34% in 1998 to 18% in 2003 and to 9% in 2007 [6]. With this brief about reactive arthritis, this review focus on basics of disease and special emphasis on diagnose and management.

EPIDEMIOLOGY

More than 40 subtypes of HLA-B27 are known; those associated with the spondyloarthropathies are HLA-B2702, B2704, and B2705 [7]. These subtypes may be geographically segregated. The subtype B2705 is found predominantly in Latin America, Brazil, Taiwan, and parts of India. It is noteworthy that subtypes HLA-B2706 and B2709 found in native Indonesia and Sardinia, respectively; may be partially protective against reactive arthritis [8]. Incidence of reactive arthritis varies greatly but has been estimated at about 3.5/100,000. The incidence reported in United States (US) Navy personnel over a 10-year period was 4 cases per 100,000 men per year. The prevalence of reactive arthritis may be relatively high among patients with AIDS, especially men who are seropositive for HLA-B27. The reactive arthritis develops in almost 75% of HIV-positive men with HLA-B27. The infections that incite reactive arthritis may vary with geographic location. For example, *Y enterocolitica* is more commonly identified in Europe than in North America and thus is responsible for more cases of reactive arthritis in countries such as Finland and Norway. The occurrence of reactive arthritis appears to be related to the prevalence of HLA-B27 in a population and to the rate of urethritis/ cervicitis and infectious diarrhoea [9]. Hanova et al, (2010) reported that, in Norway, an annual incidence of 4.6 cases per 100,000 populations for chlamydial reactive arthritis and an incidence of 5 cases per 100,000 populations for enteric bacteria-induced reactive arthritis [10].

Reactive arthritis is most prevalent among Caucasians because of the higher incidence of HLA-B27 among that ethnic group. The sex ratio is approximately equal in the postdysenteric form but is greatly male-biased in the posturethritis form [11]. A higher incidence of reactive arthritis is observed among young (ages of 20-40 year) white men, than women and children [12]. Among all 1.0 % of all men with non-specific urethritis may develop reactive arthritis [13]. The most frequent age of onset is in the early 20s, but reactive arthritis has been recognized from childhood into the sixth decade [14].

ETIOPATHOLOGY

The course of the reactive arthritis depends on the type of inducing bacteria, the presence of HLA-B27 antigen, gender and recurrence of arthritis [Table 1].

Table 1: Etiology of reactive arthritis

Causative	Descriptions
HLA-B27 gene	About 80% of people with Reiter syndrome have the HLA-B27 gene. Only 6% of people who do not have the syndrome have the HLA-B27 gene [15].
Bacterial triggers	Enteric infection with <i>salmonella</i> , <i>shigella</i> , <i>Yersinia</i> , and <i>Campylobacter</i> [16]; <i>Mycobacterium tuberculosis</i> [17].
Sexually transmitted disease triggers and	By Chlamydia- chlamydial reactive arthritis [16, 18], respiratory infection reactive arthritis [14].
Protozoan triggers	By <i>Neisseria gonorrhoeae</i> [18]. <i>Cyclospora</i> , a protozoan pathogen that causes a syndrome of diarrhoea and fatigue and prolonged gastrointestinal illness [19, 20].

Reactive arthritis is associated with HLA-B27, which a major histo-compatibility class-I (MHC-I) molecule involved in T-cell antigen presentation. Reactive arthritis results for HLA-B27 positive (75%) strong family prediction (25%) of the disease tend to develop more severe and long-term disease [21]. The exact mechanism of pathogenesis of reactive arthritis is unclear. Although recent research studies in reactive arthritis suggested some strong evidences for the pathogenesis of disease. The interaction of the inciting organism with the host (often

positive HLA-B27) leads stimulating and perpetuating an autoimmune response mediated by type 2 T helper (Th2) cells. Chronicity and joint damage have been associated with a Th2 cytokine profile that leads to decreased bacterial clearance [9].

A systemic and intra-synovial immune response to the organisms has been found with intra-articular antibody and bacterial reactive T cells. These elements produce an immune-mediated synovitis. In reactive arthritis synovitis is mediated by proinflammatory cytokines. Native T cells under the influence of transforming growth factor (TGF)- β and other cytokines, mainly interleukin (IL)-6, differentiate into Th17 effector cells, which then produce IL-17. IL-17 is one of the major cytokines elevated in the synovial fluid [22, 23]. Thus deficiencies in regulatory mechanisms can result in increased proinflammatory cytokine production and worse outcome. The Toll-like receptors (TLRs) recognize different extracellular antigens as part of the innate immune system [24]. TLR-4 recognizes gram-negative lipopolysaccharide (LPS) and downregulation of TLR-4 costimulatory receptors activity. However some study implicated that TLR-2 polymorphism associated with acute reactive arthritis [9, 25].

CLINICAL MANIFESTATIONS

The duration of reactive arthritis is considered to be chronic when it extends over 6 month.

Reactive arthritis has a high tendency to recur (15-50% of cases), particularly in individuals who are HLA-B27-positive. A new infection or other stress factor could cause reactivation of the disease [26, 27].

Arthritis or musculoskeleton symptoms

Joint symptoms may vary, ranging from arthralgia to the severe inflammation of several joints. Typically inflammation of a single or asymmetric inflammation of several joints is observed. This includes pain, swelling, stiffness, and redness of joints, usually the knees, ankles, dactylitis (inflammation of fingers) and feet. Inflammation of the sacroiliac or spine joints occurs in approximately 50% of patients, manifesting itself as an inflammatory back pain with back stiffness and buttock pain [28].

Ocular disease

Reactive arthritis may be associated with chronic recurrent ocular inflammation. Conjunctivitis can occur in all types of reactive arthritis, often as an early symptom. It is predominant pathology of the sight organ in reactive arthritis and especially in patients with reactive arthritis caused by Chlamydia. In Chlamydia trachomatis induced reactive arthritis conjunctivitis occurs within a few days of the first symptoms of urethritis and usually withdraws within a week. Conjunctivitis can relapse and take a severe course. Conjunctivitis is often painless and nonseptic, but it may also cause burning sensation and irritation of the eyes. In acute reactive arthritis, conjunctivitis is observed in 2% of patients and 96% chronic. Uveitis less common and occurs to about 10 to 20% of reactive arthritis patients with positive HLA-B27 antigen in one or more episodes. The main symptoms present are unilateral eye pain with redness, lacrimation, photophobia, and blurred vision [29]. Systemic therapy typically is required to control the ocular inflammation and to prevent progressive visual loss [30].

Urogenital lesions

The urinary tract infection is most common in Chlamydial reactive arthritis. Painful urination is quite common due to shallow ulcers on the penis in men. Inflammatory changes affecting the mucous membrane of the urogenital tract and the skin of sex organs include prostatitis, testitis and/or epididymitis in men and cervicitis in women. Marked parakeratosis with extensive neutrophilic infiltrates and large microabscesses forming a thick crust are observed. The dermal infiltrate was mixed with numerous lymphocytes and neutrophils and scattered plasma cells [31].

Gastro-intestinal tract manifestations

The reactive arthritis includes mouth sores. The lesions occur on the palate, tongue, buccal mucous membrane, lips, gums, tonsils, nasal septum and pharynx, with or without pain. Sometimes it may noted by the patients slight burning, loss of taste and mild sore throat [32]. Cuvelier *et al*, (1987), by histopathologically observed that, in 49% of cases abundant infiltration of inflammatory cells to the lining of the lamina propria of the mucosa, partial flattening of intestinal villi, and hyperplasia, infiltration and abscesses of the crypt epithelial cells. In 18% erosions of intestinal epithelium with or without granuloma are present [33].

Skin disease

Mucocutaneous involvement occurs in approximately 50% of patients with reactive arthritis. It may occur before or after the onset of oligoarthritis. The two classic cutaneous manifestations of reactive arthritis are keratoderma blennorrhagicum (skin lesions commonly found on the palms and soles) and balanitis circinata (skin inflammation around the penis in males), both of which are microscopically similar to pustular psoriasis (form of psoriasis, raised bumps on the skin that are filled with pus). Keratoderma blennorrhagicum appears 1 to 2 months after the onset of

arthritis and is present in about 10% of patients. It almost always involves the soles of the feet but may affect the legs, hands, nails, and scalp [34, 35]. With supporting this another study revealed that, a week after the appearance of the skin lesions revealed erythematous, confluent, hyperkeratotic papules and pseudopustules on the palms, soles, fingers and toes, and diffuse yellowish hyperkeratotic plaques on the soles including swelling and restricted movement of the left ankle and of the right wrist [36].

Cardiovascular risks

The patient's with reactive arthritis affecting heart problems to about 10%. Inflammatory changes leads to enlargement of aortic arch and ascending aorta, and also appearance of aortic valve regurgitation [37, 38].

Neurological diseases

Central or peripheral nervous system involvement in reactive arthritis has been well recognized, but this particular condition is very uncommon. A case report by Kim *et al.*, (2007) reported that initially presented with progressive cervical myelopathy and diagnosed as reactive arthritis 2 years later. The myelopathy was stable after treatment with methotrexate and sulfasalazine. This case suggests that reactive arthritis can present as progressive myelopathy and should be considered in the differential diagnosis of treatable myelopathies [39]. Various other researchers reported that reactive arthritis uncommonly affects the spine. There are several cases of reactive arthritis involving the cervical spine [40, 41] and lumbar vertebrae [42].

DIAGNOSIS

Diagnosis of reactive arthritis is difficult due to vast variation of the clinical features, largely empiric, relapsing courses and classical triad is present in only one third of the patient [13, 43]. The American Rheumatism Association developed in 1981 the following diagnostic criteria for Reiter's disease: an episode of peripheral arthritis of more than 1-month duration occurring in association with urethritis, cervicitis, or both [44].

Patient history

It should be assess the any history of stomach problems due to enteric infection, chronic respiratory infection or sexually transmitted diseases may be test for Chlamydia [43, 44].

Physical examination

The physician should perform examination and pay particular attention for the signs of joint involvement (arthritis), skin and mucosal changes, eye involvement and symptoms suggesting lung pathologies (sarcoidosis) [44].

Biopsy and histopathological study

The test samples of cells can be collect from throat as well as the urethra in men or the cervix in women. Histopathology examination of the skin biopsy reveals organization of epidermis and nature of inflammatory infiltrate dermis [31, 36].

Urine and stool samples for microbial tests

If evidence of previous infection detected either by serology or by cultures from urogenital or stool samples [45].

Blood test

Blood test can be done to rule other diseases and presence of the HLA-B27 gene [46]. Generally it may includes, complete blood cell count, differential leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), estimation of Chlamydia trachomatis antibodies (IgA & IgG), rheumatoid factor (RF) and others [31, 36].

Radiographic study

X-ray examinations can be done for any other abnormal findings related to arthritis. Radiographic changes are seen in more than 70% of patients with chronic reactive arthritis and are characterized by the picture of swelling soft tissues especially characteristic is so called sausage finger, periosteal ossification with exostosis, erosions on the articular surfaces and periarticular osteopenia. Less frequently erosions in small joints of the feet, hands, knees and sacroiliac joints are observed [47].

Synovial fluid analysis

This indicates arthritic joints for the demonstration of sterile inflammatory synovitis with various estimations including neutrophils (15,000 to 30,000 neutrophils/ μ L) and others [48].

MANAGEMENT

Drug Therapies

It is important for the treatment of reactive arthritis, to use physio- and kinesitherapy (treatment of disease by movements or exercise), together with pharmacological treatment. The treatment of reactive arthritis should be based on reducing pain, anti-inflammatory treatment and eradication of infection [32]. Most of drugs used in therapy of RA are suitable, under the consideration of status of reactive arthritis [49, 50]. Systemic treatment of reactive arthritis can be done with Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying agents, immunosuppressive therapy, biological agents and antibiotics. Reactive arthritis can also be managed by nutrient supplements and various well known herbal agents.

Initial treatment with NSAIDs

Generally used in lower inflammation or initial diagnostic period while prolonged therapy is recommended in case of persistent inflammation. Sometimes NSAIDs are used in combination with sulfasalazine for the effective treatment of reactive arthritis. 20-25% of patients with reactive arthritis do not feel improvement after NSAIDs, immunosuppressants may be beneficial. The commonly used NSAIDs include indomethacin, ibuprofen and naproxen [51, 52]. In some cases lumbar pain of spine and leg pain in Reiter's syndrome managed conservatively with celecoxib capsules along with dexamethasone, tripterygium glycosides and antibiotics [42].

Corticosteroids

Prednisolone can be used as maintenance therapy along with methotrexate mainly injected into painful joints to reduce inflammation [39]. Depending on the severity of disease, corticosteroids are administered either through topical, oral or intra-articular routes [14].

Disease modifying drugs (Immunosuppressants)

In case of ineffectiveness of NSAIDs in reactive arthritis, disease-modifying drugs are recommended. The most commonly used drugs in this group include sulfasalazine, methotrexate, azathioprine, cyclosporine, leflunomide [53-55].

Biological agents- Tumor necrosis factor-alpha (TNF-alpha) inhibitors

There are no randomized trials evaluating the efficacy and safety of biological agents of anti- TNF-alpha group in the treatment of reactive arthritis. The use of biological agents from the anti-TNF-alpha group is restricted to the chronic form of the disease, in which disease modifying drugs were ineffective. TNF inhibitors for the treatment of reactive arthritis include etanercept, infliximab, and adalimumab [56-58].

Antibiotics

The use of antibiotics in reactive arthritis still raises controversy. Eradication of bacteria causing reactive arthritis should improve prognosis or prevent the development of reactive arthritis. Studies have shown various effects of antibiotic use for reactive arthritis induced by genitourinary infections and different effects in Enterobacteriaceae-induced reactive arthritis cases [31, 36]. Tetracycline or ciprofloxacin for a period from 4 to 12 weeks in acute Chlamydia-induced reactive arthritis were also reported [59]. Recent *in vitro* studies showed high efficacy of using a combination of antibiotics (azithromycin and rifampicin) in eradicating Chlamydia infection [60], rifampicin and doxycycline [28]. Enterobacteriaceae induced reactive arthritis treated with three-months course of ciprofloxacin revealed the influence of the therapy on the distant course of reactive arthritis, particularly in patients with HLA B-27 antigen and may prevent the development of chronic reactive arthritis [61].

Complementary and Alternative Therapies

Although no complementary and alternative therapies have been shown to help reactive arthritis specifically, however some may help reduce inflammation and support immune system.

Adjunct therapy

Adjunct therapies include rest, heel supports, and gentle non-weight-bearing exercises. The various study revealed that, most of the chemical constituents from various herbal sources showed potent anti-reactive arthritis by reducing inflammation. Bromelain (an enzyme derived from pineapple), turmeric or curcumin (*Curcuma longa*) used in combination with bromelain, salicin (*Salix alba*), licorice (*Glycyrrhiza glabra*) and boswellia (*Boswellia serrata*). These herbal drugs are effective in the treatment of reactive arthritis by their anti-inflammatory action. Researchers further suggested that, these drugs are risk in bleeding, and there will be cautions usage of these drugs along with NSAIDs as the preliminary agents for the treatment of reactive arthritis. So it is advised to use anti-rheumatoid drugs should be ulcerprotective and they may be good drugs for reactive arthritis [62-64]. Some nutrition and supplements like shark cartilage or chondroitin sulfate (800 - 1,200 mg per day, divided in 2 - 4 doses) may help provide pain

relief over time, although it has been studied only in osteoarthritis. Omega-3 fatty acids (1,000 - 1,500 mg two times per day of fish oil) help reduce inflammation and are good for your heart [65, 66].

CONCLUSION

Reactive arthritis often goes unrecognized and may result in significant morbidity. Reactive arthritis should be considered if a patient has experienced with minimal manifestations including any history of conjunctivitis, arthritis, or urethritis. Depending on the symptoms, proper diagnosis should be performed to find the cause for reactive arthritis. Various herbs showed effective in reactive arthritis by their anti-inflammatory nature but not promising. As the available therapies are not promising and management of the disease is complex; further investigations are required to find effective therapeutic agents to treat reactive arthritis.

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