Reactive Arthritis

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Abstract

Reactive arthritis is a disease affecting mostly young adults. Owing to a greater general awareness the diagnosis has become more common during recent years. It is well established that ReA is caused by an infection, mostly in genetically susceptible individuals. The pathogenetic mechanisms are still poorly understood, and the treatment rests mainly on anti-inflammatory drugs or steroids. Vigorous and early treatment of the triggering infection may prevent the development of ReA but this is rarely possible in everyday clinical practice. Despite its name, the disease should be considered as a general disorder that affects not only the joints. The prognosis is not as good as earlier believed, and relapses or chronic development are not unusual.

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For practical clinical use, reactive arthritis can be defined as a sterile joint inflammation that develops after a distant infection. In the past the term Reiter's disease was widely used but it is generally agreed that ReA is a more appropriate moniker. Still, those cases in which the triad of symptoms – arthritis, sterile urethritis and eye inflammation is met – are often called Reiter's disease. Rheumatic fever and in some instances Lyme arthritis may also be included in ReAs in a broader sense.

Recent observations regarding, for example, the presence of microbial components in the joints of patients with ReA have demonstrated the need for improved diagnostic criteria [1]. A classification of the whole spondylarthropathy group, including also psoriatic arthritis and ankylosing spondylitis, was proposed by a European Spondylarthropathy Group in 1991 [2]. This classification was actually established to facilitate early diagnosis and to include also atypical cases, as pointed out by Gran [3].

Intensive research during the last two decades has provided an impressive amount of new information regarding ReA. Yet, the pathogenesis is still not fully understood and therefore no proper therapy or prophylaxis exists. In this review the current knowledge on ReA as well as the therapeutic possibilities are discussed.

ReA = reactive arthritis

Pathogenesis

Reactive arthritis is definitely an infectious disease. A previously healthy but genetically predisposed individual who contracts a suitable triggering infection will develop ReA after some time. This pathogenetic process spans the incubation time of the triggering infection and its clinically overt phase, followed a few days to a couple of weeks later by full-blown ReA. The list of microbes known to cause ReA is lengthy [1,4,5]. Table 1 presents the most common microbes. In most instances the primary infection affects either the gastrointestinal or the urogenital tract; hence the terms enteroarthritis or uroarthritis. It is well established that inflammatory bowel diseases such as ulcerative colitis or Crohn's disease may lead to ReA, even when they are clinically silent [6]. Also, respiratory tract infections by *Chlamydia pneumoniae*, for example, may play the triggering role in ReA [4,7–9]. An important aspect to keep in mind in clinical practice is that the triggering primary infection may pass with very mild symptoms or may even be symptomless, and its severity is not at all related to the severity of the later ReA.

An important factor associated with the susceptibility of an individual to ReA is HLA-B27. Furthermore, it appears that in B27-positive individuals the disease is more severe and the

Table 1. Causes of ReA

Enteric infections	**Various parasites**
*Campylobacter**	*Ascaris*
*Clostridium**	*Giardia lamblia*
*Salmonella**	Filarial worms
*Shigella**	*Schistosoma*
*Yersinia**	*Strongyloides stercoralis*
Urogenital infections	*Taenia saginata*
*Chlamydia**	**Disease states**
Neisseria	Acne
Ureaplasma	Celiac disease
Upper respiratory tract infections	Cystic fibrosis
*Chlamydia pneumoniae**	Infective endocarditis
Streptococcus pyogenes group A	Inflammatory bowel disease
Other infections	Intestinal bypass
Borrelia	Suppurative hidradenitis
Brucella	
Mycobacterium	
Staphylococcus	
Viruses	

* Triggers ReA predominantly in HLA-B27-positive individuals

tendency for chronicity greater than in those who are B27 negative [10]. For over two decades extensive efforts have been devoted by several groups to clarify the mechanisms behind this association. The different HLA-B27 loci have been characterized in minute detail and the peptides bound by this structure analyzed. Yet, it is still not known exactly how HLA-B27 works in the pathogenetic process. It is noteworthy that by far not all B27 positive individuals develop ReA, even if they contract a suitable triggering infection. On the other hand, B27-negative individuals may have ReA that may well develop into severe or chronic forms [11]. It is also apparent that the disease can be divided into a B27-associated and non-associated form [5]. The cases triggered by enteric infections such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter* or *Clostridium difficile*, as well as uroarthritis triggered by *Chlamydia trachomatis* belong to the former category, while rheumatic fever and Lyme disease belong to the latter.

Clinical picture

The clinical picture of reactive arthritis varies from mild arthralgias to severely disabling conditions. This disease, in spite of its name, is not restricted to the joints but affects several different organs and tissues. This indicates that the pathogenetic process is of general immunological character [12]. The most common manifestations are listed in Table 2. It is noteworthy that although the triggering infection may affect either the urogenital or intestinal mucosa, later an inflammation at these sites such as sterile urethritis or bowel inflammation adds to the actual clinical picture. Skin lesions vary, the most severe being keratodermia blenorrhagica or palmoplantar pustulosis. Macroscopically and microscopically these lesions are similar to psoriasis. Various eye inflammations, often unilateral, are not limited to anterior uveitis but may affect different parts of the eye. Prompt diagnosis of uveitis by split lamp is necessary for rapid institution of treatment in order to avoid irreversible damage to the eyesight. Visceral manifestations are rare except in rheumatic fever. The main symptoms are linked to the joints. Enthesopathy, tendinitis and frank asymmetric oligoarthritis are typical manifestations. Typically, the ReA patient seeks first-time medical help for a suddenly swollen knee, ankle or other large joint. Sometimes the disease affects small joints symmetrically, and in these cases differentiation from rheumatoid arthritis is difficult.

Table 2. Clinical manifestations of ReA

Symptoms of the locomotor system	**Urogenital manifestations**
Arthralgia	Circinate balanitis
Arthritis	Sterile urethritis
Enthesitis	Cystitis
Tendinitis, tendovaginitis	Prostatitis
Osteitis, hyperostosis	Cervicitis
	Salpingo-oophoritis
Symptoms of skin and mucous membranes	**Ocular lesions**
Various psoriasis-like manifestations	Conjunctivitis – episcleritis, keratitis
Keratodermia blenorrhagica	Corneal ulcerations
Pustulosis palmoplantaris	Anterior uveitis
Nail dystrophies	**Other manifestations**
Oral buccal erosions and inflammation	Gut inflammation
	Other visceral manifestations such as carditis or nephritis

Diagnosis is based on the clinical picture and on the anamnestic information. A history of infection is often obtained. Especially regarding small outbreaks of enteric infections, other family members may have more prominent symptoms than the individual with ReA. As mentioned above, the primary infection may have passed quite unnoticed and therefore a positive anamnesis cannot be considered an absolute requirement for the diagnosis.

Laboratory diagnosis

The usual laboratory tests such as erythrocyte sedimentation rate, leukocyte count and C-reactive protein indicate an inflammatory process but are too non-specific to permit diagnosis. If possible a joint fluid sample should be taken and analyzed carefully, including cell counts and bacteriological examinations. It should be noted that in the early phase a differential diagnosis between bacterial and reactive arthritis is extremely difficult, as described by Kortekangas et al. [13]. In the acute phase, when the patient seeks medical help for the first time, blood and synovial fluid leukocytosis is similar in both groups, as are blood values. Within a few days the ReA picture usually changes, with the joint fluid granulocytosis transforming into lymphocytosis.

Once the arthritis is well developed, isolation of the triggering microbe is usually impossible. However, in uroarthritis patients, polymerase chain reaction for demonstration of chlamydial DNA in a first-void urine sample or uterine cervical smear should be tried; and in enteroarthritis it may be useful to take a stool culture. The diagnosis depends largely on positive serological demonstration of antibodies directed against *Yersinia*, *Campylobacter*, *Salmonella*, or *Chlamydia*. In patients with ReA, the immunoglobulin A class antibodies, particularly, tend to be significantly elevated and remain so for a long time [12]. The IgM class antibodies – typical of recent infection – perform well in agglutination, which is not the case regarding IgA class antibodies. Therefore, an enzyme immunoassay methodology that permits an assessment of antibodies belonging to the different immunoglobulin classes is recommended for a later and more accurate diagnosis. Other tests such as immunoblotting have also been used in different countries [14]. Unfortunately, serology is not available for the identification of all possible triggering agents. Thus, *Shigella* infections do not give rise to an antibody response that would be helpful in the diagnosis of ReA.

Ig = immunoglobulin

The joint fluid is by definition sterile. Bacterial degradation products, including lipopolysaccharide, may be present intra- or extracellularly. PCR methodology has resulted in positive demonstration of chlamydial DNA and RNA from the synovium and synovial fluid of ReA patients [15–17]. It has also been demonstrated that synovial fluid mononuclear cells react in proliferation tests against the triggering microbe or its components, but this methodology is too elaborate for routine clinical work and is more valuable for basic studies on the pathogenesis of ReA [18–20].

Roentgenological studies are not contributory for the diagnosis, and classical X-ray pictures yield little information. Magnetic resonance imaging reveals enthesitis and tendinitis, but the benefit for everyday practical work is negligible.

Clinical course and prognosis

ReA is considered a disease with a self-limiting course. While it is true that the prognosis is good for a few weeks or months for even severe forms of the disease, several studies have demonstrated that relapses are rather common. Uveitis, especially, has a strong tendency to be activated by non-specific factors. Chronic arthralgias, tendon inflammations and enthesopathies tend to cause discomfort and affect the patient later on [10,11,21,22]. Severe deforming disease with erosions is extremely rare, but development of sacroiliitis and mild forms of ankylosing spondylitis are more common than earlier thought [6,22]. In our institution we have seen a case in which ankylosing spondylitis and secondary amyloidosis led to the death of a young boy whose disease had originally been triggered by *Yersinia pseudotuberculosis* [23].

It is noteworthy that the severity of the initial clinical picture does not indicate the risk of later chronicity. There is a general feeling that uroarthritides may have a higher tendency to lead to chronic low back inflammatory conditions, but no formal proof has yet been presented.

Management of ReA

Since the clinical severity of ReA varies, the therapy has to be tailored accordingly [24]. The patients are often young previously healthy persons who have a fear of a progressive disabling disease. Therefore, it is essential that the physician properly inform the patient about the disease, that the prognosis is usually good but that there is some tendency to relapses and later chronic arthralgias. Rest is advisable but the patient should move if the condition permits. Upon recovery, heavy use of the joints, e.g., in sports. should be avoided for some time as non-specific mild traumas may initiate a relapse.

The cornerstone of therapy is non-steroidal anti-inflammatory drugs. Since their clinical and side effects vary with each individual, it may be necessary to test a few in order to select the best. It is important to inform the patient that the drug should be used in sufficient dose and for a sufficient time, even after the worst symptoms have disappeared. Since the patients are often young, they are reluctant to take pain killers. They should be told that the anti-inflammatory effect, rather than the analgesic one, is important in ReA.

Corticosteroids are used in different ways. Intra-articular steroids are useful when only one or a few joints are affected. An injection leads to rapid disapppearance of the inflammation and the patient may return to normal activities. If symptoms reappear, the injection can be repeated several times. It is imperative to exclude purulent arthritis and to follow the patient carefully because of the risk of infection. In Finland, intra-articular steroids are used extensively and infectious complications are extremely rare. If many joints are affected or if the patient is generally ill, systemic corticosteroids should be used. Starting with a high daily dose, e.g., prednisolone 40–60 mg, they are rapidly tapered down according to the clinical condition. Finally, the drug should be continued for a few weeks at a low dose. Corticosteroids are useful in cases of relapse as well. They should be avoided in chronic arthralgias since their therapeutic effect is poor at that stage.

The role of antibiotics has been the focus of keen interest [24,25]. There are several theoretical reasons supporting their use. ReA is definitely caused by an infection, and several findings indicate that the triggering microbe persists somewhere in the organism, maintaining an immune reponse [12,26]. Also, the demonstration of chlamydial DNA or RNA from the joint indicates the presence of viable *Chlamydia* [15–17]. In two instances the value of antibiotics is firmly established – in the primary and secondary prevention of rheumatic fever, and in the treatment of borreliosis. If a *Borrelia* infection is treated with appropriate antibiotics in an early phase, development of later Lyme arthritis can be inhibited. It must be noted that in these cases the antibiotics are not used for actual treatment of the ReA but for its prevention. Some authors suggest that the reactive disease triggered by a beta-hemolytic *Streptococcus* infection should be divided into true rheumatic fever and post-streptococcal ReA. In a recent article on this question, the authors concluded that further prospective investigation is needed to determine whether penicillin prophylaxis should also be used in those cases considered post-streptococcal ReA, as it is in rheumatic fever [27].

Evidence regarding the effect of antibiotics in enteroarthritis and uroarthritis is somewhat different. Definite agreement exists that short-term antibiotics are not useful in ReA triggered by an enteric infection. Later, long-term treatment may be applied. A recent study indicates that patients who received ciprofloxacin in an oral dose of 500 mg twice daily had a tendency towards faster remission and relief of pain than those receiving placebo. However, the number of patients was rather small – 7 in the ciprofloxacin and 11 in the placebo group [28]. Recently, two larger, systematic double-blind randomized placebo-controlled studies on the effect of a 3 month course of ciprofloxacin on ReA were carried out. Neither study could demonstrate a beneficial effect of the antibiotic [29,30]. The

PCR = polymerase chain reaction

overall conclusion at present therefore is that antibiotics do not have a therapeutic role in ReA.

These observations are also supported by data from an experimental model with *Yersinia*-induced ReA in the rat. When ciprofloxacin was given immediately after intravenous inoculation of the microbe or when the arthritis was developing, a definite effect was seen, but when the antibiotic was given later it had no effect whatsoever. Actually, some rats turned out to become late carriers of *Yersinia*, secreting bacteria into the stool [31,32].

For uroarthritis, the picture is not quite as clear. An interesting study by Bardin and coworkers [33] in an Inuit Eskimo society demonstrated that proper and prompt treatment of new genitourinary tract infections dramatically reduced relapses of ReA. It is important to stress here that the treatment should rather be considered as secondary prophylaxis. In an earlier study, Lauhio et al. [34] noticed that lymecycline had a slightly beneficial effect in patients with uroarthritis. Observations on long-term ciprofloxacin treatment indicate that some beneficial effect could perhaps be obtained in *Chlamydia*-triggered ReA. However, so far the number of such patients has always been too small to allow any firm conclusion [29].

Conclusion

Overall, clinical and experimental studies have clearly demonstrated that early and vigorous treatment of a triggering infection before the development of ReA is effective. However, in real life this goal can almost never be reached. The patient seeks help for joint inflammation, the initial infection has already passed, and antibiotics are no longer effective. At this stage the only possibility is to proceed according to the therapeutic outlines discussed above. It is important for the patient to know that although he or she may suffer from various locomotor symptoms in the future, there is no serious risk of morbidity.

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