Reactive arthritis: can't see, can't pee, can't climb a tree...

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Reiter’s disease, also known as reactive arthritis, is a seronegative HLA-B27-associated autoimmune disease, characterised by oligoarthritis of large joints with additional ophthalmic and urological manifestations. Many will recall the *aide-mémoire* 'can't see, can't pee, can't climb a tree' from their medical school days. This article describes the history and aetiology of Reiter’s disease, along with its treatment and prognosis, and reminds readers to be vigilant for its characteristic signs and symptoms.

Figure 1. Anterior uveitis is seen in 12–37% of patients with reactive arthritis

Hans Conrad Julius Reiter, born 1881, was an eminent physician and a contemporary of Hitler. His work while Honorary Professor of Social Hygiene included a book on racial hygiene: *Deutsches gold, gesundes leben – frohes schaffen* (German gold, healthy life – glad work). He was subsequently convicted of war crimes. It is unsurprising, therefore, that there is mounting pressure to strip Reiter of the honour of carrying the title of this disease.

Discrediting his politics is easy; discrediting his scientific rigour and talent is more difficult. The triad of urethritis, conjunctivitis and arthritis was described by several people, including Benjamin Brodie in 1818. But it was not until 1916, when Reiter described a case of non-gonococcal urethritis, conjunctivitis and arthritis suffered by a young officer with bloody diarrhoea, that this distinct arthritis came to the attention of the scientific community. He also discovered a non-pathogenic form of *Treponema pallidum* (the causative agent of syphilis) enabling his development of the ‘Reiter Complement Fixation Test’ for its detection. He went on to describe the spirochaete responsible for Weil’s disease. Furthermore, Reiter also implemented strict anti-smoking laws in Germany, which were extremely progressive for the time. Charming and loved amongst his students, he was a corresponding member of the Royal Society of Medicine in London. He lectured in rheumatology until his 80s and died aged 88.

Eponyms are gradually drifting out of favour in medicine. This, coupled with Reiter’s past, has led to the disease being categorised more simply as ‘reactive arthritis’.

**AETIOLOGY AND EPIDEMIOLOGY**

Reactive arthritis classically presents with the triad of asymmetrical joint pain and swelling, urological and ophthalmic manifestations two to four weeks after infection, with specific viruses or bacteria. Contrary to traditional teaching, studies have shown that only one third of reactive arthritis patients present with the full triad of symptoms.

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Epidemiological data for reactive arthritis are lacking due to the heterogeneity of disease manifestation, and prevalence studies are few in the absence of definitive diagnostic criteria. The incidence has been estimated to be in the region of 0.6–27:100 000 in Scandinavia, where most of the studies on reactive arthritis have been carried out. Similar to the aetiology of other spondyloarthopathies, 75% of patients are HLA-B27 positive. There is a preponderance towards the male sex and those of Caucasian origin, between the ages of 20–40 years old.

The aetiology of reactive arthritis is classically divided into enteric and venereal subgroups to reflect the causative micro-organisms:

- Commonest enteric agents: Shigella, Salmonella, Yersinia, Escherichia coli
- Commonest venereal agents: Chlamydia, Gonorrhoeae

More recently, groups in Finland, India and France have found that some cases of reactive arthritis appear to have been precipitated by urinary tract infections. We have also found similar cases in our hospital that support this view.

**PATHOGENESIS**

'Reactive' refers to the temporal association between infection and the onset of one or more of the 'triad' of clinical manifestations. Infection is thought to result in cross-reactivity between antibodies produced during the infection and cells that express HLA-B27 in the joints, eyes and genitourinary tissues. The exact mechanism remains unclear. Joint aspirates in patients are often culture-negative, supporting the autoimmune rather than infective aetiology, although this may simply reflect a deficit in our current screening modalities. A recent report from Malaysia even describes an unusual case of reactive arthritis following instillation of Bacillus Calmette-Guérin (BCG) for bladder cancer.

With the exact pathogenesis still unclear, the American College of Rheumatologists set out a series of sensitivity and specificity criteria aimed at aiding the diagnosis of this condition (Table 1).

The diagnosis of reactive arthritis remains simple urinary tract infections. The diagnosis of gonoococcal or non-gonococcal urethritis (NGU) is made through microscopic assessment of first-pass urine or by urethral smear. Gram stain analysis remains the gold standard for detection of gonococcal urethritis. The presence of polymorphonuclear leucocytes is otherwise pathognomonic for NGU. Antibiotic treatment is empirical, with reference to local policy guidelines. Contact tracing/treatment is recommended.

If untreated, urethritis may progress (in males) to epididymitis, orchitis, prostatitis and chronic pelvic pain. Long-term, this is complicated by the increased risk of urethral stricture formation, leading to incomplete bladder emptying and urinary retention. Serial flow rates, post-void residuals with urodynamic and/or cystoscopic investigations will elucidate worsening mechanical obstruction of the urethra. Any such outflow obstruction can predispose further genitourinary infection and ultimately propagate persistent lower urinary tract symptoms in varying degrees of severity.

In females, urethritis is closely associated with the development of cervicitis, salpingitis and pelvic inflammatory disease. Infection with the obligate intracellular venereal pathogen C. trachomatis may be asymptomatic. Long-term, this aetiology and its sequelae have significant potential implications on fertility if unidentified and untreated.

**OPHTHALMIC MANIFESTATIONS**

The opthalmic manifestations of reactive arthritis include conjunctivitis, anterior uveitis, episcleritis, scleritis and keratitis, similar to other seronegative HLA B27-associated arthropathies, including psoriasis. Less common presentations include retinal vasculitis, optic neuritis and glaucoma.

Conjunctivitis is one of the hallmarks of reactive arthritis and is seen in 33–100%

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Asymmetric oligoarthritis</td>
<td>44.3</td>
<td>95</td>
</tr>
<tr>
<td>Sausage digit</td>
<td>26.6</td>
<td>99</td>
</tr>
<tr>
<td>Heel pain</td>
<td>51.6</td>
<td>92.2</td>
</tr>
<tr>
<td>Inflammatory dorsal or lower back or buttock pain</td>
<td>71.4</td>
<td>77.3</td>
</tr>
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Table 1. Sensitivity and specificity of 'distinctive' clinical features in reactive arthritis
of cases, usually early on in the disease, with spontaneous remission after around two weeks. Symptoms can be mild, with injected, dry eyes, or severe, with intense pain, oedema and purulent discharge.

The second most common ocular manifestation is uveitis (iritis, iridocyclitis), seen in 12–37% of patients (see Figure 1). It is characterised by photophobia, impaired vision, scleral injection and hypopyon (sterile exudate within the anterior chamber). Slit-lamp examination of the posterior segment of the eye is warranted to ensure that there is no evidence of posterior uveitis. One of the complications of uveitis associated with reactive arthritis is the formation of posterior synechiae (adhesion of the iris to the surface of the lens or vitreous body), which can lead to angle-closure glaucoma and blindness.

Management of ocular complications varies depending on the severity of presentation. Mild conjunctivitis is treated conservatively, with an emphasis on ocular hygiene, whilst cycloplegics, such as atropine, may be administered for comfort for iritis. Severe ocular complications may necessitate topical, oral and/or intravenous steroid treatment. Immunosuppression is the mainstay of treatment in patients with recurrent symptoms or flare-ups of reactive arthritis. The use of topical antibiotics is controversial, but some studies have found evidence that topical azithromycin was effective when applied for a period of two weeks in Chlamydia-associated conjunctivitis in reactive arthritis.

OTHER MANIFESTATIONS
Skin manifestations, although less common, have also been described in the literature. Keratoderma blennorrhagicum, the formation of hyperkeratotic lesions on the palms and soles of the feet, is typical (Figure 2). These lesions can coalesce to form pustules, which may be clinically and histologically indistinguishable from pustular psoriasis.

Erythematous lesions may form on the oropharyngeal mucosa in up to 60% of patients, typically the tongue, leading to erosions and bleeding. A small proportion of patients with chronic reactive arthritis will present with cardiac manifestations, including aortitis and aortic regurgitation.

MANAGEMENT
Treatment is symptomatic and not curative, as two-thirds of patients have a self-limiting course. Patients should be advised to rest in the acute phase and start physiotherapy once this has subsided. NSAIDs are used for joint pain, together with short courses of steroids if required. Disease-modifying agents, including methotrexate and sulfasalazine,

KEY POINTS
- Reactive arthritis is likely under-diagnosed and requires an increased awareness of proposed diagnostic criteria amongst clinicians to minimise long-term morbidity
- There remains a persistent emphasis on early identification (and treatment) of antecedent infections. These should be culture-proven, if possible
- Patients with recurrent manifestations or chronic reactive arthritis pose more of a challenge for clinicians, and should be under the care of a rheumatologist
- Sexual history should be included within systems review in all patients under 40 with new onset joint pain in the absence of trauma
- Clinicians are encouraged to signpost high-risk patients towards STI screening
- The most common ophthalmic manifestation is conjunctivitis, for which conservative management is generally sufficient, although some advocate the concurrent use of topical azithromycin. For more severe manifestations, such as uveitis and scleritis, there may be a role for immunosuppressants
have been used under the supervision of rheumatologists to great effect.\textsuperscript{14} The efficacy of antibiotics to target the initial infection is still controversial; studies have found no effect with azithromycin\textsuperscript{10} and some effect with combined antibiotic therapy.\textsuperscript{14} The current consensus is that antibiotic therapy does not alter the course of the disease.

**PROGNOSIS**

Whilst the majority of patients can expect to recover fully from the disease within three to five months, there are reports of patients who suffer a chronic course of potentially destructive arthritis. Only a limited number of studies have looked at this. One study by the European League Against Rheumatism followed 152 patients. They described low disease activity in all patients, 32 weeks after initial presentation, as assessed by clinician and patient global assessments.\textsuperscript{10} Another Finnish study found that up to 19\% of patients remained symptomatic for over one year.\textsuperscript{3}

**Declaration of interests:** none declared.

**REFERENCES**