Sexually-acquired reactive arthritis

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Reactive arthritis is the most frequent cause of acute peripheral arthritis in young men. The aetiopathogenesis of reactive arthritis is reviewed, together with the varied clinical features. Finally the treatment and prognosis of this challenging condition are discussed.

Commenting on an acute gout-like arthritis following sexual exposure, Hippocrates said: 'A youth does not suffer from gout until after sexual intercourse.' In 1507, Van Forest described a patient with arthritis of the knee in association with urethritis (Sharp, 1972). In 1818, Sir Benjamin Brodie first noted the triad of arthritis, conjunctivitis and urethritis, and 100 years later Hans Reiter described identical symptoms in a soldier following acute dysentery.

The term 'reactive arthritis' was first suggested in the 1960s, reflecting the fact that this type of arthritis followed both enteric and genital infections, although the joint effusions seen in such patients, despite being intensely inflammatory, were sterile (Ahvonen et al, 1969). *Chlamydia trachomatis* is now recognized as the primary pathogen associated with this sexually-acquired reactive arthritis (Kousa, 1982; Amor, 1983).

The condition was frequently noted to have a familial element and eventually the strong association with the HLA-B27 gene was discovered (Brewerton et al, 1973). Very quickly the clear overlap of symptoms and signs of reactive arthritis with those of ankylosing spondylitis led to its inclusion in the family of 'sero-negative spondylo-arthritides' (Wright and Reed, 1964).

AETIOLOGY

Since the early 1990s there has been increasing evidence that chlamydia, which can be viable but is difficult to culture, may be present in the joint of reactive arthritis patients. Structures that look like whole chlamydia (Schumacher et al, 1988), chlamydial DNA (Gerard et al, 1997) and chlamydial RNA (Rahman et al, 1992) have been isolated from the joint in acute reactive arthritis. The significance of this is unclear, especially as *C. trachomatis* has been detected in the joints of asymptomatic subjects (Schumacher et al, 1999).

The role of HLA-B27 in the development of reactive arthritis remains unclear, as reactive arthritis is well recognized in B27-negative patients too. Class I antigens present antigenic peptides to cytotoxic lymphocytes and this action may be important. It has also been suggested that HLA-B27 influences the handling of bacteria by phagocytic cells (Kapasi and Inman, 1994).

In enteric reactive arthritis, both Yersinia and Shigella share amino acid sequences with HLA-B27, suggesting possible cross-reactivity (molecular mimicry) (Lahesmaa et al, 1991). Such cross-reactivity may lead to tolerance and persistence of organisms.

Similarly to the reticulo-endothelial system, joints are prime sites for the lodging of circulating infectious agents. Thus genetic factors may affect the initial phagocytosis of chlamydia, type of spread, and its action in the joint (Schumacher, 1998). Research on all these factors continues.

CLINICAL FEATURES

Reactive arthritis is a condition of young people, peaking between 16 and 35 years (Arnett, 1982). Although it is more common in males (Keat, 1983), it has been well described in women (Neuwelt et al, 1982). It is the most common cause of acute peripheral arthritis in young men (Arnett, 1982). Acute synovitis begins 1–3 weeks after the initial urethritis and is predominantly a lower limb, asymmetrical oligoarthritis. Knee effusions are frequently observed and can be so tense that joint rupture occurs (Weese and McCarthy, 1969). Fusiform dactylitis ('sausage digits') is particularly characteristic of the spondylo-arthritides. Enthesitis (inflammation at ligament or tendon attachments to bone) is also

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common and is most often seen as an Achilles tendonitis or plantar fasciitis. As well as peripheral arthritis, thoracic and lumbar spine pain may occur along with buttock pain (suggesting sacroiliitis). Disability can be considerable and compounded by fatigue, sweats and anorexia.

The classic triad of arthritis, urethritis and conjunctivitis does not always occur — urogenital symptoms may be asymptomatic, or limited to a mild and painless urethral discharge. More severe infections can occur and in men may be accompanied by prostatitis (Amor, 1998), while in women by cervicitis, which is usually marked by a vaginal discharge. It is important to emphasize that symptoms and signs of sterile urethritis may also occur following enteric infection and need not imply sexually-acquired reactive arthritis. Conversely, diarrhoea occurs in venereally-acquired disease in about 30% of patients (Weinberger et al, 1962).

Mucocutaneous lesions, although not frequent, are very specific. Circinate balanitis is an erythematous painless lesion of the glans, and similar lesions can occur on the hard and soft palate, gingiva, tongue and buccal mucosa. These lesions are often overlooked by patients and must be specifically searched for. The less common keratoderma blenorrhagica, which resembles pustular psoriasis, occurs on the soles and palms (Hancock, 1969). A differential diagnosis of gonococcal arthritis should be suspected if dermatitis is present, as approximately 75% of these patients have skin lesions on the trunk and extremities.

Conjunctivitis may be mild (patient feeling grittiness in the eye), or more marked, with a sterile discharge (Popert et al, 1964). Rarely, serious eye disease develops with keratitis, corneal ulceration or even uveitis (the latter is more common in late or recurrent disease). Other visceral involvement includes cardiac problems (conduction defects in early stages (Weinberger et al, 1962) and aortic incompetence in later stages (Csonka et al, 1961)), and respiratory disease (pleural and pulmonary infiltrates; Thiers and Pinet, 1950).

LABORATORY INVESTIGATIONS

Typically a very high erythrocyte sedimentation rate and high levels of C-reactive protein are seen; leucocytosis and normochromic or normocytic anaemia may also be present (Hall and Finegold, 1953). HLA-B27 testing is not necessary except to support a less certain diagnosis, but would be expected to be positive in around 80% of cases and may contribute to prognosis (Keat et al, 1983).

Synovial fluid analysis and culture should be performed to rule out septic arthritis. High numbers of polymorphonuclear leucocytes are typically seen (Ellis and Bereston, 1959), and protein levels will be high, but synovial fluid and tissue cultures will be negative. Urethral and cervical swabs should be analysed for *C. trachomatis* using micro-immunofluorescence with specific antisera. Enzyme-linked immunosorbent assay (ELISA) tests appear useful for detecting antichlamydia antibodies in serum and synovial fluid (Bas and Vischer, 1998). If diarrhoea continues stool cultures are necessary to rule out an enteric pathogen.

Testing for human immunodeficiency virus (HIV) should be considered, as reactive arthritis is sometimes seen in HIV-positive individuals.

MANAGEMENT

Once a diagnosis of reactive arthritis has been established treatment aims to reduce pain and inflammation, thereby improving function until the disease enters a natural remission. At this stage rest, and occasionally splinting and/or physiotherapy, should be part of the management plan. Non-steroidal anti-inflammatory medication in full dosage is necessary and proton pump inhibitors may also be required in patients with a history of peptic ulceration. When joint sepsis has been excluded, aspiration of larger joints followed by intra-articular steroids is usually beneficial. If there is a possibility of septic arthritis, it is advisable to delay steroid injection until culture results are available. Unlike rheumatoid arthritis, there is no evidence that oral prednisolone is helpful (Schumacher, 1998), and the author does not use it routinely, although intravenous methylprednislone may be valuable in severe joint inflammation. In patients who cannot tolerate anti-inflammatories, intramuscular steroids can be helpful.

The role of antibiotics in chlamydia-associated reactive arthritis is controversial — although a short course of tetracycline is commonly prescribed, there is no evidence that it improves outcome (Bardin and Schumacher, 1992). Lauhio et al (1991) found a 3-month course of lymecycline to be beneficial but this has not become standard practice. A 3-month study of reactive arthritis found ciprofloxacin was superior to placebo, but results were not significant because of a small sample size (Sieper et al, 1999). Genitally-acquired reactive arthritis requires referral to a genitourinary medicine clinic and contact tracing.

In patients who have persistent arthritis after 6 months, sulphasalazine may have a disease-modifying action (Clegg et al, 1996), and methotrexate and azathioprine may also be beneficial in resistant disease (Lally and Ho, 1985; Calin, 1986).

PROGNOSIS

The prognosis in sexually-acquired reactive arthritis is thought to be worse than for arthritis follow-

ing enteric infection, which may be because reinfection is more common (Csonka, 1958). Generally the first oligo-articular episode subsides within 6 months of onset (Amor, 1998), but follow-up studies show that 20–70% of patients still have exacerbations of arthritis after 1 year. The frequency of sacroiliitis is approximately 33%, but can be as high as 58% in patients who are HLA-B27 positive (Wollenhaupt et al, 1995). Of these patients, 15% will develop the axial lesions of ankylosing spondylitis (Amor, 1998).

A more severe outcome with recurrent systemic disease is seen in 1% of patients, especially those with keratoderma blenorrhagica (Amor et al, 1995). Both balanitis and psoriatic lesions may take months to settle. Even in chronic disease, destructive joint damage is not universal (unlike in rheumatoid arthritis), although bone proliferation and periostitis are prominent (Resnick and Niwayama, 1988).

CONCLUSIONS

The aetiology of *C. trachomatis*-induced reactive arthritis remains unclear. Chlamydial antigens and nucleic acids have been isolated in joints of patients with reactive arthritis and in asymptomatic individuals. The condition is the commonest cause of acute inflammatory arthritis in young men; most have a good prognosis, but a significant number develop chronic systemic disease. HM

Conflict of interest: none.

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KEY POINTS

- *Chlamydia trachomatis* is the primary pathogen associated with the sexually-acquired form of reactive arthritis, a condition of young people.
- The classic triad of arthritis, urethritis and conjunctivitis does not always occur.
- A very high erythrocyte sedimentation rate and high levels of C-reactive protein are seen, with 80% of cases being HLA-B27 positive.
- Synovial fluid analysis and culture should be performed to rule out septic arthritis and urethral and cervical swabs should be analysed for *C. trachomatis.*
- Treatment aims to reduce pain and inflammation by use of non-steroidal anti-inflammatory agents and/or intra-articular steroids, until the disease enters natural remission. The role of antibiotics is controversial.
- The condition remains the most common cause of acute inflammatory arthritis in young men and a significant number develop chronic systemic disease.