

Non-genital manifestations of *Chlamydia trachomatis*

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Chlamydia trachomatis is the commonest treatable sexually transmitted infection (STI) in Europe. There is a 10% prevalence in women aged 16–24 years attending UK contraception and antenatal clinics or general practices, peaking at 13% at age 18.¹ Chlamydial infection rarely causes systemic disease. The infection is primarily urethral or cervical/tubal and is asymptomatic in the majority of patients of both sexes;² thus it is endemic. Because *C. trachomatis* is so widespread, most general physicians will occasionally encounter a patient with extragenital manifestations (Table 1).

Presentation and pathogenesis

C. trachomatis infects moist mucosal surfaces; it produces covert damage principally by triggering a localised cell-mediated immune response which is magnified by repeated exposure to infection. The most important extragenital manifestations of sexually acquired reactive arthritis (SARA)³ (part of the Reiter's syndrome triad of arthritis, urethritis and conjunctivitis) and perihepatitis⁴

depend on an atypical reaction to *C. trachomatis*. Although poorly understood, this is determined by the patient's genotype and immunological/hormonal status, and probably mediated through a delayed cell-mediated immune response to chlamydial heat-shock protein (chsp60)⁵ which is homologous with human hsp60. Reiter's syndrome also develops in response to enteric infections including *Campylobacter spp* and *Yersinia enterocolitica*, which both express hsp60.

The human leucocyte antigen (HLA) B27 gene is expressed in 6–8% of Caucasians in the general population but is present in 70–80% of Caucasians with sexually acquired Reiter's syndrome, rising to 90% of those with chronic symptoms. Overall, 1–3% of men with chlamydial urethritis develop Reiter's syndrome compared with about 25% of those who express HLA B27. There are several subtypes of the protein and wide ethnic variations in prevalence. This is presumably why Reiter's syndrome is less common in some groups, for example West Africans. Most investigators have reported a lower incidence of the condition in women than in men. However, since many of the studies have been done in predominantly male populations, it is unclear whether there is a true sex bias.

Eyes

C. trachomatis was discovered in 1907 by Halberstaedter and von Prowazek who noticed unusual intracellular inclusion

bodies when examining material scraped from the eyes. They called them 'chlamydozoa' because they were draped around the cell's nucleus (κλαμψις = cloak). Direct inoculation of chlamydiae into the eye can lead 4–12 days later to the development of inclusion conjunctivitis, usually in only one eye and usually mild, but which can cause an obvious mucopurulent discharge. There is often non-tender pre-auricular lymphadenopathy, and the inflammation under the upper eyelid may sometimes present as ptosis. Serovars (biological subtypes) A–C of *C. trachomatis* cause chronic follicular conjunctivitis and conjunctival scarring (trachoma), a leading cause of blindness in many developing countries. These serovars are rare in the UK; those which cause genital infection (D–K) are not usually associated with trachoma.

Chlamydial conjunctivitis

If chlamydial conjunctivitis is suspected, swabs should be taken for direct immunofluorescence or polymerase chain reaction, depending on laboratory

Key Points

Chlamydial infection is a common sexually transmitted infection with an incidence of approximately 10% in adults under 25 years

Most genital infections are asymptomatic

Systemic complications are rare but may be associated with asymptomatic genital infections

Reiter's syndrome and its *forme fruste*, sexually acquired reactive arthritis, occur most frequently in HLA B27-positive individuals following a chlamydial urethritis

Perihepatitis complicates 20% of cases of chlamydial salpingitis and may be confused with acute cholecystitis

Ectopic pregnancy can occasionally present with symptoms of mild gastroenteritis

KEY WORDS: arthritis, chlamydia, *Chlamydia trachomatis*, perihepatitis, Reiter's syndrome

Table 1. Sites infected by *Chlamydia trachomatis* and clinical manifestations.

Genital surfaces	Extragenital surfaces	Non-mucosal manifestations
Urethra	Conjunctiva	Uveitis
Epididymis	Pharynx(?)	Plantar fasciitis
Rectum	Liver and spleen	Keratoderma blennorrhagia
Cervix	Appendix	Circinate balanitis
Endometrium	Peritoneum	
Endosalpynx	Synovial membrane	
Pelvic peritoneum		

facilities. If *C. trachomatis* is confirmed, it is likely to be secondary to a coexisting genital tract infection. Treatment is as for an uncomplicated genital infection (doxycycline 100 mg twice daily for 7 days or azithromycin 1g stat). A sexual history should be obtained, and screening for other STIs undertaken. Sexual contacts will need to be treated. The local sexual health/genitourinary medicine clinic will help with this.

Chlamydial conjunctivitis also occurs in neonates when a child is born through an infected cervix. The presentation, 7–14 days after delivery, is often confused with the ubiquitous ‘sticky eye’. Systemic erythromycin is required as the nasopharynx is also involved; topical treatment alone may result in the child presenting with infant chlamydial pneumonia months later. The mother and her sexual partner(s) also need investigation and treatment.

Serious eye involvement

More severe eye involvement including anterior uveitis and corneal ulceration has been reported in up to 12% of Reiter’s syndrome cases.⁶ This can progress to posterior uveitis or to retinitis with detachment or the development of posterior synechiae. A patient with conjunctivitis who is thought to have Reiter’s syndrome should be seen by an ophthalmologist for slit-lamp examination to exclude uveitis. Uveitis can be treated with a mydriatic and steroid eye drops.

Gastrointestinal system

C. trachomatis can infect the throat and rectum as a result of sexual contact, but it rarely causes symptoms and is much less common than *Neisseria gonorrhoeae* at these sites. The mouth is involved in up to 30% of cases of Reiter’s syndrome. The shallow painless ulcers in the mouth or on the lips require no specific treatment.

Perihepatitis

Perihepatitis (Fitz-Hugh–Curtis syndrome (FHCS)) (Fig 1) produces right upper quadrant (RUQ) pain identical to that of

cholecystitis. Many patients have no pelvic pain. Originally presumed to be a rare complication of gonorrhoea, FHCS occurs in about 20% of women with chlamydial salpingitis. These women express the highest titres of hsp60 antibody and are rarely found to be taking the combined oral contraceptive pill.⁴ Pain may be bilateral as perisplenitis occurs occasionally. In the acute phase, a liver friction rub may be heard; minor liver function abnormalities are present in about 20%. Exceptionally rarely, small bowel may herniate through the adhesions. FHCS is rare in men, in whom chlamydial spread to the liver capsule is via the lymphatics.

Treatment of perihepatitis is as for pelvic infection,⁷ with attention paid to partner management to prevent reinfection.⁸ Acute RUQ pain usually resolves on initial antibiotic therapy but mild discomfort may persist. Adhesiolysis is rarely indicated.

‘Normal’ appendicectomy

The highest rate of ‘normal’ appendicectomy occurs in 17–18 year old women, coinciding with the age peak of chlamy-

dial infection.¹ It is thought that at least some cases of apparently normal appendices are manifestations of a chlamydial infection⁹ which causes plasma cell serosal inflammation (periappendicitis).

Ectopic pregnancy

Ongoing, persistent chlamydial infection causes most, if not all, ectopic pregnancies in young women.¹⁰ Rarely, mild generalised peritoneal irritation from a bleeding ectopic is indistinguishable from gastroenteritis. This misdiagnosis is a principal cause of the 5–7 deaths in the UK per annum; it can be avoided by taking a careful menstrual and contraceptive history, having a high index of suspicion, and by pregnancy testing.

Skin

Non-genital skin involvement occurs in 20% of people with sexually acquired Reiter’s syndrome. The classic lesion is keratoderma blennorrhagica which resembles pustular psoriasis and typically occurs on the soles of the feet. A more widespread psoriasiform rash can also occur. Thickening of the nail beds due to

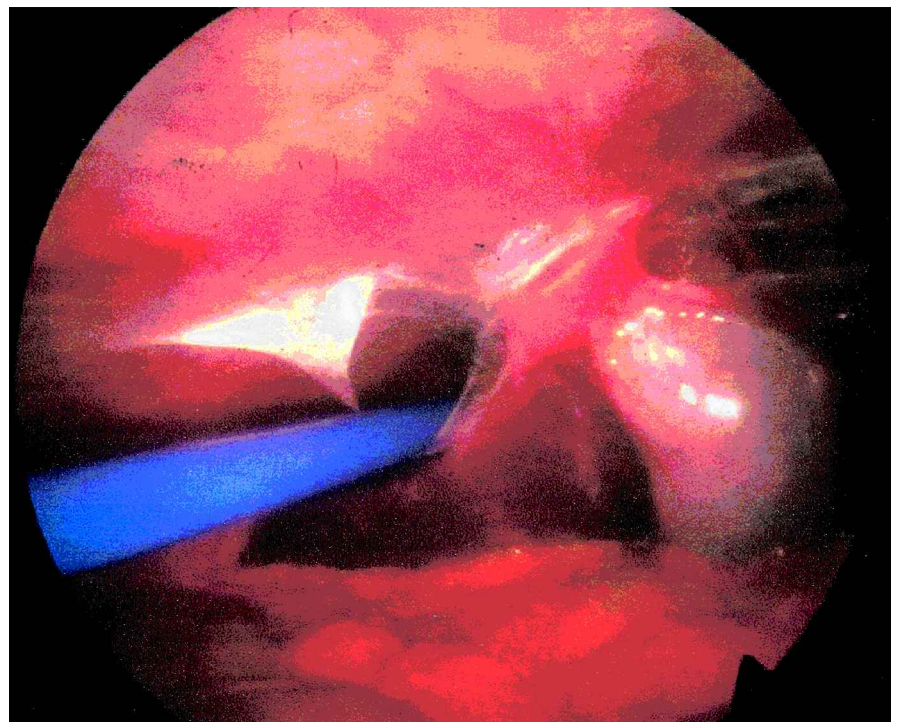


Fig 1. Fitz-Hugh–Curtis syndrome showing perihepatic violin-string adhesions to diaphragm and normal gall bladder. © Peter Greenhouse.

hyperkeratosis can result in a brownish discolouration of the nail. The skin changes should be treated in the same way as psoriasis (ie with emollients, topical steroids and/or calcipotriol). More severe cases should be referred to a dermatologist.

Musculoskeletal system

Many people with Reiter's syndrome have symptoms in a limited number of sites, perhaps only in the joints. *C. trachomatis* is associated with 35–69% of cases of SARA. The extent of disease is varied. Initially, there can be widespread synovitis or tendinitis, the inflammation then becomes localised to a few joints, typically the knees and ankles where effusions may develop. Sacroileitis occurs in about 10% of cases; it is often detected only radiologically and the spine is rarely affected. Inflammation of tendon insertions (enthesitis) is common, with the Achilles tendon and plantar fascia the usual sites affected.

It is unclear how *C. trachomatis* causes arthritis. Chlamydial nucleic acid has been found in synovial membrane biopsies,¹¹ so it seems likely that after genital infection the bacteria are disseminated throughout the body. T cells reactive to chlamydial antigens can be detected in people with SARA. Presumably HLA B27 (and other HLAs associated with reactive arthritis) interact with the T cells in some aberrant way, but there is no consensus about how this happens.

Treatment

Chlamydial joint symptoms should be treated as for an uncomplicated genital infection. Although chlamydiae may persist despite treatment,¹² there is no convincing evidence that longer courses of antibiotics have any effect on musculoskeletal symptoms. These symptoms can usually be successfully managed with rest and non-steroidal drugs. Intra-articular injections of steroids may be useful for more persistent mono- or oligoarthritis, and physiotherapy can prevent muscle wasting during episodes of immobility.

People with more severe arthritis

should be referred to a rheumatologist.³ Systemic steroids may be used if there is widespread joint involvement but their effect is short-lived. Disease-modifying drugs such as sulphasalazine and methotrexate are other useful second-line agents. Symptoms resolve in 2–6 months in most patients, but 17–35% have symptoms which persist for more than a year and symptoms will return in 50%. A small proportion are permanently disabled, usually by erosive disease affecting the feet.

Other systems

Many people with acute Reiter's syndrome complain of general malaise, fever, lymphadenopathy, anorexia and weight loss. Asymptomatic proteinuria and haematuria occur in up to 50%, and glomerulonephritis and immunoglobulin (Ig) A nephropathy can also develop. Effects on the heart range from mild asymptomatic ECG abnormalities in up to 30%, to rare tachycardia, complete heart block, myocarditis, pericarditis, and aortitis with valve incompetence and congestive cardiac failure. Neurological involvement is unusual, but documented complications include peripheral neuropathy, hemiplegia and meningoencephalitis. Other uncommonly reported manifestations include pleuritis, pneumonitis, thrombophlebitis, amyloidosis, subcutaneous nodules and thrombophlebitis – all these are rare, occurring in less than 1% of cases.

Infant pneumonia is a rare complication of perinatal transmission of chlamydial infection. Generally presenting as a mild, subacute atypical pneumonia around 2–3 months, it is diagnosed if there are high titres of chlamydial IgM. Erythromycin is the treatment of choice.

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