Syphilis: an update

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Clin Med 2003;**3**:209–11

Syphilis is caused by *Treponema pallidum* (TP), a fragile spiral motile organism. At the infectious stage it rarely causes life-threatening or serious illness. Natural history studies undertaken in Oslo (1890–1910) and Tuskegee in the US (1932) suggest that up to 35% of patients with early syphilis will develop serious neurological, cardiovascular or gummatous disease if untreated. Organisms almost identical to TP, *T. pertenue* and *T. carateum*, cause yaws and pinta, respectively. *T. pallidum*, *T. pertenue* and *T. carateum* are indistinguishable microscopically and all give positive results on standard serological tests for syphilis. However, yaws and pinta affect skin and bone almost exclusively, and are generally found only in patients from endemic areas (tropical and subtropical regions). Their prevalence has diminished dramatically since the advent of mass penicillin treatment.

Many accept that syphilis was imported into Europe from the New World after 1492. However, skeletal remains from recent archaeological digs in the UK show changes suggestive of syphilitic osteitis (Fig 1(a) and (b)). Their antiquity appears to predate the discovery of the New World by approximately 100 years.[1]

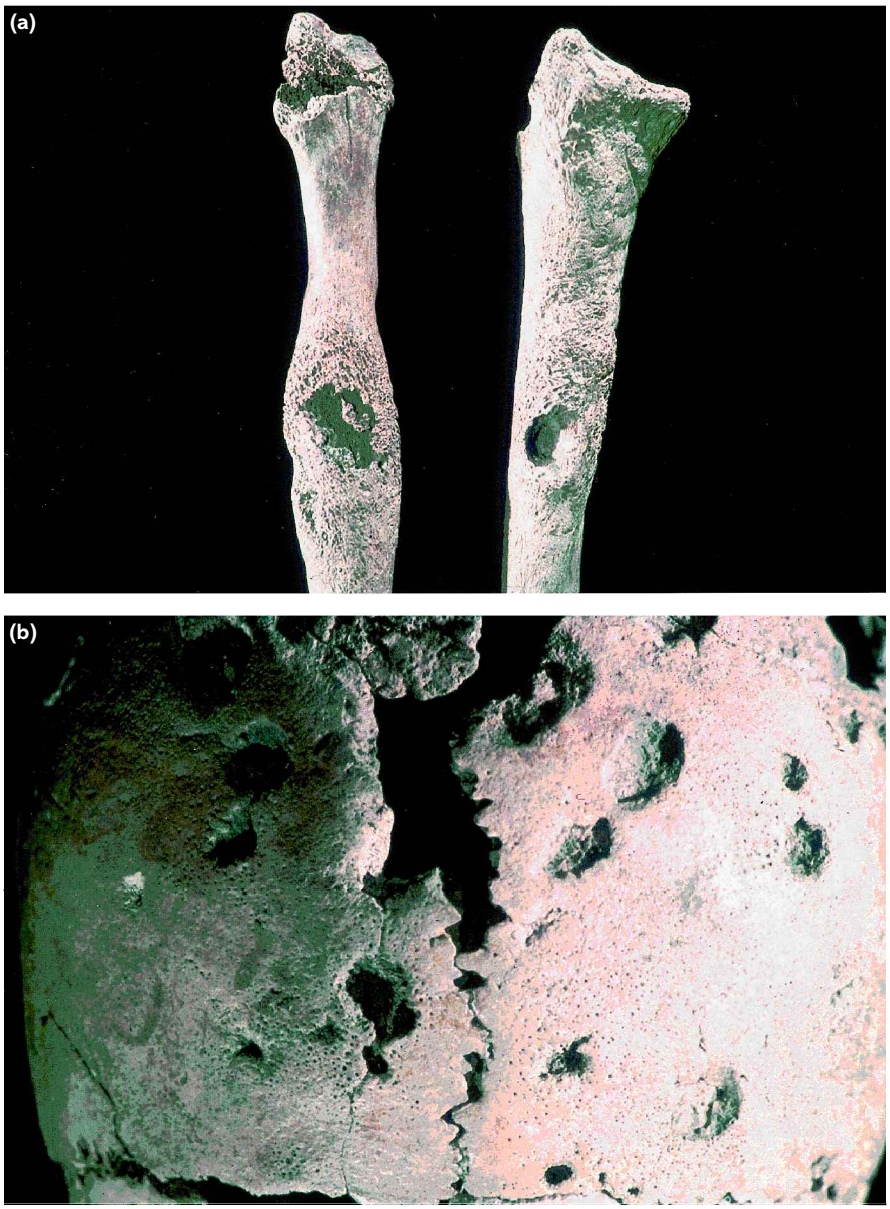

Fig 1(a) and (b) Osseous remains from the UK pre-1492, suggestive of syphilis (reprinted courtesy of Dr Charlotte Roberts, University of Durham).

Epidemiology

By the time of the First World War, serological tests and microscopic identification enabled accurate estimates of syphilis outbreaks to be made. Lengthy, but effective, bismuth and arsenic treatments, together with the changing social climate and contact tracing, led to a significant fall in the rates of infectious syphilis in the UK between the wars. However, by the time of the Second World War, 20,000 new cases of infectious syphilis were reported annually and one in a hundred pregnant women was seropositive on antenatal screening.[2] By the early 1950s with the introduction of penicillin treatment, there were only about 1,000 new cases of infectious syphilis per annum. From the 1960s until the early 1980s there was another resurgence of infectious syphilis in the UK (about 2,000 new cases per year), as well as an influx of patients with positive serology from the West Indies and the Indian subcontinent. General concern and fear of HIV in the UK led to a dramatic fall in case numbers in the following decade, but between 1995 and 2000 there was a 145% increase in incidence in England, Wales and Northern Ireland. This is a higher rate of growth than for any other sexually transmitted disease, even though the number of cases reported in 2000 was only 333.[3] To put this in context, in England in 1998 there were 0.3 new cases of early syphilis per 100,000 compared to 900 per 100,000 in the Russian Federation in 1996.[4]

Recent outbreaks

An outbreak in Bristol in the late 1990s was among heterosexuals and associated with crack cocaine use.[5] Other ongoing outbreaks have been in Manchester,[6] Brighton[7] and London.[8] Most outbreaks are among gay men who have high-risk intercourse (unprotected anal intercourse) with anonymous partners in saunas and easily accessible 'cruising grounds'. Sex after brief introductions in internet chat rooms seems to be a route of infection in a number of cases. Many patients also have concurrent HIV infection. Although orogenital sex poses a lower risk for HIV transmission, it is a common route of syphilis acquisition. New cases of neonatal congenital syphilis have recently been described.[9] Attempts at containment of the recent syphilis epidemic in the UK have been through both conventional contact tracing and social networking.

Clinical features

Syphilis is microbiologically a systemic disease from the onset. Despite this, the primary stage usually produces an ulcer (chancre) 9–90 days (mean 21 days) after intercourse. This starts as a papule that eventually breaks down to form an indurated, usually painless, ulcer. The common sites are the external genitalia and anus, but the oral cavity, breast and relatively symptomatically silent areas such as the cervix, rectum and pharynx may also be affected. Without treatment, the primary sore heals in 3–6 weeks. Diagnosis at this stage may be undertaken by identification of TP in fluid from lesions examined by dark-field microscopy.

Secondary syphilis

Secondary syphilis usually commences about 4–10 weeks after the appearance of the chancre, but the two stages are sometimes concurrent. The patient usually presents with a macular or maculopapular rash affecting the entire trunk, and in particular the palms and soles. The lesions are generally discrete, red or reddish-brown, 0.5–2 cm in diameter. Contrary to what was written in old textbooks, dermatological lesions of secondary syphilis may present in any form, including pustules and vesicles, and may be itchy. Alopecia is well recognised, as are mucosal lesions that appear as painless aphthous ulcers. Condylomata lata are TP-laden white/grey lesions found in moist areas (axilla, anus, genitalia). Asthenia, weight loss, sore throat, fever and myalgia are common. There is often generalised lymphadenopathy and bone pain due to periostitis. About 20% of cases have subclinical non-icteric hepatitis with disproportionately raised serum alkaline phosphatase levels. Secondary syphilis may also cause nephrotic syndrome. Iritis and anterior uveitis are not uncommon, but usually asymptomatic.

Cerebrospinal fluid (CSF) changes are present in up to 40% of secondary syphilis cases; some patients may have clinical meningo-encephalitis, particularly those with concomitant HIV infection. Cases of early syphilis associated with HIV have been reported where there is rapid onset of meningitis, cranial nerve lesions (particularly optic and eighth nerves) and cerebrovascular accidents.[10,11]

Treponemicidal and treponemostatic antibiotics (penicillins, tetracyclines, macrolides) given to treat a coexisting condition may obscure this clinical picture, considerably confusing the diagnosis. Co-trimoxazole or quinolones do not affect TP. Without treatment all the clinical manifestations of secondary syphilis resolve spontaneously in 3–12 weeks. In the pre-antibiotic era, 25% of patients had one or more episodes of recrudescence of the secondary symptoms.[12] This has been observed more recently in patients with concurrent HIV who had inadequate treatment for syphilis.[10,11]

Other stages of syphilis

Latent syphilis. If left untreated, most patients will reach a latent stage in which no clinical symptoms or signs are present. Latent syphilis in the first two years of the infection is defined as early latent; at this stage, the Venereal Disease Research Laboratory (VDRL)/rapid plasmin reagin (RPR) titres are high (see below) and a relapse may still occur.

Late syphilis is defined two years after the acquisition of the infection and is considered a non-infectious stage.

Late latent syphilis is diagnosed by finding positive treponemal serology with no evidence of a prior negative test within the previous two years and no symptoms or signs of late syphilis. Reaginic serology titres are low or even negative.

Key Points

- **The incidence of infectious syphilis in the UK has greatly increased since 1995, mainly in cities and commonly among gay men**
- **Syphilis is a systemic disease from the outset. It usually presents early with a painless penile ulcer, or later with a maculopapular rash, lymphadenopathy and condylomata lata**
- **Diagnosis is confirmed serologically, at first by specific treponemal screening and confirmatory tests (eg enzyme immunoassay and *Treponema pallidum* particle agglutination test), subsequently by non-specific serology (eg rapid plasmin reagin test) to gauge disease activity**
- **Clinical suspicion of neurosyphilis should be confirmed by analysis of a clear specimen of cerebrospinal fluid**
- **The cornerstones of management are rapid investigation and treatment, tracing and treating sexual contacts, and education about safer sex**

KEY WORDS: diagnosis, epidemiology, syphilis

Tertiary syphilis. In about one-third of untreated individuals tertiary syphilis develops a number of years after early infection. Three main clinical pictures may coexist:

- cardiovascular syphilis
- neurosyphilis, and
- gummata.

Neurosyphilis. The classic clinical pictures of tabes dorsalis and general paresis are well described in most standard texts. However, because of widespread antibiotic usage the clinical presentation of neurosyphilis may be atypical (eg a *forme fruste* with hyporeflexia, absent ankle jerks and pupillary abnormalities).[13]

CSF examination of patients with positive blood serology and atypical neurological signs is mandatory. One or more positive CSF measurements indicating syphilis (see below) with no other explanation for the neurological picture suggests modified neurosyphilis.

Serological and cerebrospinal fluid testing

Serological tests for syphilis may be classified in two groups:

1 The reaginic or non-treponemal tests which detect non-specific treponemal antibody (ie VDRL and the RPR).

2 The specific treponemal tests such as the TP particle agglutination assay (TPPA), TP haemagglutination assay and enzyme immunoassay (EIA).

Screening for syphilis should be carried out using a sensitive and specific assay, either the EIA or the TPPA. After confirmatory specific treponemal serological testing, a reaginic test (VDRL or RPR) is used to assess the stage and degree of activity of the disease.[14] Up to 15% of patients with primary syphilis will be seronegative at initial presentation, so a second set of tests is always advisable when syphilis is suspected. This is also recommended to confirm positive results.

If neurological involvement is suspected, CSF testing is indispensable. This should be performed on clear fluid. If a bloody tap is obtained, the blood-stained portion should not be used for serological tests, although microscopic red cell presence in a clear specimen will not give false positive results.[15] A positive RPR in CSF is diagnostic of neurosyphilis but its absence does not exclude the diagnosis. Specific treponemal tests positive in CSF are highly sensitive but not as specific.

Interpretation of the clinical picture, together with the CSF results (eg absent knee jerks with no other known cause and positive TPPA in the CSF), needs sensible and careful clinical management (see above).

Management and treatment

The cornerstones for management of syphilis are:[16]

- education about safer sex practices
- reminding physicians and general practitioners of the symptoms and signs of the disease, and
- rapid investigation and treatment of patients and their contacts.

Patients who have suggestive symptoms, signs or serological tests should ideally be referred to a genitourinary physician for comprehensive management.

Treatment of syphilis is beyond the scope of this article but is well covered in the UK National Guidelines.[17] Treatment is inexpensive. Daily injections of procaine penicillin have been used for many years in the UK, although compliance is easier with the long-acting benzathine penicillin. HIV-associated syphilis is still treated with benzathine penicillin in the US, but in the UK this and neurosyphilis are usually treated with high-dose procaine penicillin or amoxicillin plus probenecid.

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