Don't forget about syphilis: the great pretender

Syphilis, caused by an infectious spirochaete *Treponema pallidum*, acquired sexually, congenitally or rarely via blood transfusion, has historically been stigmatised and feared by society. Early epidemics of the 'grande verole' caused severe disease with high mortality rates and spread throughout Europe before becoming less virulent. Known as the 'great pretender' because of its numerous manifestations, William Osler told his students that 'it is the only disease which they are required to know thoroughly. Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you' (Chen et al, 2015).

The side effects of treatments, including mercury poisoning, arsenic toxicity and deliberate infection with malaria, were terrible and it was not until the advent of penicillin in the 1940s that a pivotal point was reached with hope of confining syphilis to the history books. Two case reports in this issue report unusual manifestations of syphilis, a case of aortic regurgitation by Fleri-Soler et al (https://doi.org/10.12968/hmed.2018.79.4.232) and a case of pulmonary nodules by Roberts et al (https://doi.org/10.12968/hmed.2018.79.4.230), reminding clinicians that knowing syphilis and its manifestations remains relevant today. If you do not consider it, you do not test for it; if you do not test for it, you will not find it.

Epidemiological overview

The prevalence of syphilis plummeted to less than 1% with the widespread availability of penicillin and became forgotten as a differential diagnosis in much of the developed world. However, prevalence has always varied significantly with rates exceeding 6% in some areas, such as sub-Saharan Africa (Kenyon et al, 2016). An estimated 2.1 million pregnant women have active syphilis annually and 69% will have an adverse pregnancy outcome (Hawkes et al, 2011).

Syphilis also illustrates how closely politics, economics and health are entwined; collapse of the former USSR contributed to the resurgence of syphilis in the Russian Federation and former Eastern Bloc countries while urbanisation and social change facilitated the increase in syphilis cases in China (Chen et al, 2015). Nor is there room for complacency in the UK or Europe as Roberts et al and Fleri-Soler et al demonstrate: syphilis cases among Londoners have soared by 165% since 2010, with 90% of cases being diagnosed in men who have sex with men, many of whom are co-infected with HIV (Public Health England, 2016), alongside a smaller rise among heterosexuals (Public Health England, 2016). Congenital syphilis in the UK remains relatively rare but is not unknown. In 2016 there were three cases where the UK-born mother had acquired syphilis later in pregnancy (Public Health England, 2017).

Implications for general and hospital physicians

Doctors' understanding of the clinical manifestations of the disease pre-dates penicillin and has traditionally been divided into primary, secondary, latent and tertiary syphilis, with some overlap of these stages. The average incubation period is 21 days, but can range from 10–90 days. The chancre associated with primary syphilis classically presents as a painless anogenital ulcer with moderate regional lymphadenopathy which heals over 3–8 weeks (Kingston et al, 2016); however, painful and/or multiple lesions before resolution are not unusual and may be more common with HIV co-infection. Dark ground microscopy, and more recently polymerase chain reaction from swabs from the ulcer, can aid diagnosis and help differentiate the cause from herpes simplex virus.

Secondary syphilis usually occurs 6–12 weeks after infection of untreated syphilis and usually several weeks after the ulcer has healed, although both may also occur concurrently. It is a multi-system disorder with most patients noting a maculopapular rash (Mindel et al, 1989) and lymphadenopathy. Rarer manifestations include hepatitis, headaches, meningitis, iridocyclitis, arthritis or arthralgia, glomerulonephritis, splenomegaly, condylomata lata, alopecia and perceptive deafness (Mindel et al, 1989; Kingston et al, 2016). Latent syphilis is asymptomatic and only detected by positive serological tests for syphilis. Differentiating between early (within 2 years of infection) and late latent disease based on clinical history and any available serological result is important as treatment differs for the two stages.

Tertiary syphilis occurs in approximately a third of untreated patients, and occurs several decades after initial infection. Around 15% develop gummatous disease (granulomatous lesions with a necrotic core affecting mainly the skin and bones) and 10% develop cardiovascular disease in the form of damage to the ascending aorta leading to aortic valve regurgitation and, more rarely, coronary ostia and saccular aneurysms (Kingston et al, 2016), much like that described in the case by Fleri-Soler et al. Gummatous and cardiovascular disease are now rare in the UK.

Neurosyphilis, which occurs at any stage, is an important differential diagnosis for a number of neurological syndromes, with treponema invading the CNS in 25% of cases in the early stages of infection. It may present with meningo-vascular disease, brainstem and/or cranial nerve disorders (such as otosyphilis) or with general paresis or tabes dorsalis several decades later. There is some evidence that neurosyphilis is more common and possibly has a more accelerated progression in HIV co-infection

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(Tipple, 2015). All patients with syphilis and neurological symptoms should have a brain computed tomography or magnetic resonance imaging scan and undergo a lumbar puncture for CSF examination. Syphilis should remain an important differential in young people with stroke, cognitive decline, those presenting with unusual auditory symptoms, uveitis and those with meningitis, particularly if a sexual history suggests potential risk of syphilis acquisition. Neurosyphilis is becoming more common and as such Public Health England, which undertakes surveillance of syphilis at sexual health services in England via the genitourinary medicine clinic activity dataset (GUMCADv2) sexually transmitted infection surveillance system, has applied for approval from NHS Digital to make the reporting of ocular syphilis and otosyphilis mandatory.

Diagnosis

The choice of screening test is important and is based on serological testing. Treponemal tests such as *Treponema pallidum* particle agglutination (TPPA) and IgM/IgG enzyme immunoassay become positive early in infection and remain positive, thus being unable to distinguish past from current infection. The enzyme immunoassay is also prone to false-positive results (e.g. in low-prevalence populations) and cannot differentiate syphilis from other treponemal diseases such as yaws, pinta and bejel. Non-treponemal tests, such as rapid plasma reagin are quantitative and can detect active syphilis, but can miss early syphilis and may also have false positive reactions in other conditions (e.g. in pregnancy and autoimmune disease).

As the enzyme immunoassay and TPPA are usually positive lifelong after treatment the titre increase of the rapid plasma reagin test is the only useful serological to diagnose re-infection. In the UK, screening is with enzyme immunoassay and then TPPA for confirmation and rapid plasma reagin titres for monitoring. In suspected primary syphilis, chancres can be swabbed for polymerase chain reaction testing or dark ground microscopy can be undertaken in settings where expertise is available, as per UK British Association for Sexual Health and HIV guidelines (Kingston et al, 2016).

Treatment

Clear guidelines exist in the UK for the treatment of syphilis at various stages (Kingston et al, 2016), with a longer duration of treatment in later stages being recommended because of the presumed slower division of treponemes. Parenteral penicillin remains the treatment of choice for syphilis with doxycycline as second-line therapy for patients reporting penicillin allergy. Given the degree of macrolide resistance in the UK, azithromycin and erythromycin should be avoided. All patients diagnosed with syphilis should be referred to their local genitourinary medicine services for treatment, sexually transmitted infection screening (particularly testing for HIV) and sexual partner management.

Conclusions

It is over 110 years since the discovery of the *Treponema pallidum* and the broad range of manifestations of early and late syphilis continue to be seen. The organism still cannot be cultured and so serological testing remains a cornerstone of diagnosis. Furthermore, despite syphilis being curable with a single dose of safe, highly efficacious and well-tolerated intramuscular penicillin with no signs of resistance after over 70 years of use, the world is now in the midst of a significant syphilis epidemic that shows no signs of abating.

Since 2013 unprecedented cuts to public health funding from local authorities in England has led to reduced access to genitourinary medicine services. Many patients may find themselves presenting to other services which may not typically see syphilis so vigilance and liaising with local genitourinary medicine services for diagnosis and management is as important today as in Osler's time – if not more so. **BJHM**

KEY POINTS

- Syphilis may be forgotten but it is not gone and there has been a resurgence in infections particularly among men who have sex with men, a large proportion of whom are HIV positive.
- The classic painless chancre of primary syphilis may be altered in the context of co-infection with HIV, and testing should be undertaken if there is a history of possible exposure to syphilis.
- Syphilis is the 'great pretender' and may present in a myriad of ways. While syphilis classically presents with a chancre or a rash, it is crucial to consider syphilis in the differential diagnosis in a broad range of syndromes and elicit any risk of possible syphilis contact when taking a history.
- Testing correctly is important with serological testing usually consisting of a screening enzyme immunoassay test, confirmatory treponema pallidium particle agglutination assay and a rapid plasma reagin test to assess disease activity and guide treatment.
- Treatment dosing and duration depends on staging and is outlined in guidelines, with penicillin G remaining at the forefront of treatment despite having been used for over 70 years.

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