Neurosyphilis in HIV

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Abstract: Syphilis is a resurgent sexually transmitted infection in the UK which is disproportionately diagnosed in patients living with HIV, particularly men who have sex with men. Evidence exists to suggest that syphilis presents differently in patients with HIV, particularly in those with severe immunosuppression. Progression to neurosyphilis is more common in HIV co-infection and can be asymptomatic, often for several years. Symptoms of neurosyphilis vary but can include meningitis, meningovascular disease, general paresis and tabes dorsalis. Debate exists surrounding in which circumstances to perform a lumbar puncture and the current gold standard diagnostics have inadequate sensitivity. We recommend a pragmatic approach to lumbar punctures, interpretation of investigations, and when to consider treatment with a neuropenetrative antibiotic regimen.

THE CHANGING FACE OF SYPHILIS

Syphilis, caused by the spirochaete bacterium *Treponema pallidum,* has seen a resurgence in high-income countries in recent years, particularly among men who have sex with men(1). The widespread availability of penicillin in the United States and other industrialised countries following World War Two resulted in rates of syphilis falling from 76 per 100,000 population in 1945 to 4 per 100,000 in 1955-57. After this period syphilis became concentrated within men who have sex with men and incidence surged during the 1980s HIV/AIDS epidemic(1). In response to the fear induced by the epidemic, changes in sexual behaviour caused another decline until recently where rates have risen rapidly again(1, 2). In the United States during 2014-2015 syphilis occurred in 7.5 cases per 100,000, the highest rate since 1994(3). Similar trends were seen in England where in 2016 the number of cases was 5920 (Figure 1)(4), 12% higher than the previous year and the highest number of new diagnoses since 1949, with 80.9% of cases reported in men who have sex with men(2).

SYPHILIS INFECTION

Syphilis infection involves a number of stages. Primary syphilis classically presents 9-90 days after infection with a single, non-tender genital ulcer called a chancre which represents the first site of *T.pallidum* invasion. If untreated, primary infection progresses to secondary syphilis, typically 12 weeks, but sometimes up to 12 months after initial infection. The classic presentation of secondary syphilis is a rash which typically involves the trunk, may involve the hands or feet and may be accompanied by condylomata lata, wart-like lesions around the anogenital region. Latent syphilis results when both primary and secondary syphilis are not treated and is defined by serological proof of infection but no symptoms. It is divided into early and late latent syphilis, with early latent syphilis infectious and late latent syphilis, defined in the UK as more than two years after infection, found to generally be non-infectious (5, 6).

Syphilis will progress to tertiary disease in one third of patients without treatment roughly 20-40 years after primary infection(5). Tertiary syphilis involves a severe and self-destructive

immune response to a persistent low level burden of *T. pallidum*(5). This can present as cardiovascular syphilis, gummatous syphilis, late benign syphilis or neurosyphilis(6). It is important to emphasise that neurological symptoms can occur during any phase of infection and therefore neurosyphilis should only be considered tertiary when presenting in the late-latent period(5). Primary, secondary and early latent syphilis are collectively grouped together as early syphilis and late latent and tertiary syphilis are grouped together as late syphilis.

NEUROSYPHILIS

Neurosyphilis is a broad term used to describe the direct invasion of *T pallidum* into the nervous system and can affect the brain, spinal cord and peripheral nerves(7). Approximately 25-40% of patients will have 'neuroinvasion' at some point, typically during the primary or secondary stage of infection, but the majority will spontaneously clear the infection from the cerebrospinal fluid (CSF) without requiring treatment for neurosyphilis and potentially without having any symptoms(8). In patients whose immune system is unable to clear the infection, neurosyphilis will occur and this can also present with or without symptoms, the latter form known as asymptomatic neurosyphilis(7). There exists great debate around the topic of asymptomatic neurosyphilis which is discussed below.

Syphilis is often referred to as 'the great imitator' and it can present in countless ways. The clinical manifestations of neurosyphilis are similarly varied and patients may remain asymptomatic for years. Levels of central neurological involvement can be classified into meningeal, vascular or parenchymatous forms with direct invasion of *T. pallidum* possible at each of these sites (9). Meningeal and vascular neurosyphilis are inflammatory processes which frequently coexist (meningovascular neurosyphilis), particularly in the early years of infection(10). Meningeal involvement can present as aseptic meningitis with symptoms such as headache, photophobia and neck stiffness and can lead to complications such as cranial nerve palsies(9). Vascular syphilis can affect the arterial supply of the brain or spinal cord resulting in ischaemic stroke and, depending on the arterial territory involved, can cause different neurological deficits. Neurosyphilis should therefore always be considered as a differential diagnosis in any patient with ischaemic stroke of unknown aetiology, particularly in young people(9). Parenchymal neurosyphilis is neurodegenerative in nature and can manifest as general paresis characterised by memory deficit, emotional lability, psychosis or tabes dorsalis (also known as syphilitic myelopathy) in which patients may develop sensory ataxia and neuropathic pain in the lower limbs(11, 12). Parenchymal changes tend to arise years to decades after initial infection and due to the widespread availability and prescribing of penicillin are now extremely rare(11, 13). A fourth, distinct and rare form of central neurosyphilis can emerge in gummatous syphilis which causes space occupying lesions which may result in seizures, focal neurological signs, raised intracranial pressure or progressive paraparesis or quadriparesis(9). Involvement of the peripheral nervous system is not the focus

of this review and is less common but can include polyradiculopathy and peripheral neuropathy(14).

THE SYNERGISTIC RELATIONSHIP BETWEEN HIV AND SYPHILIS

HIV and syphilis affect similar patient groups and in 2002 the United States Center for Disease and Control Prevention (CDC) reported the incidence of syphilis to be 77 times greater in HIV infected individuals than that of the general population(15). This is of particular significance because HIV and syphilis have a synergistic relationship wherein syphilis can increase the risk of HIV transmission and acquisition whilst HIV can affect the presentation, diagnosis, progression and treatment response of syphilis(16). A large body of the evidence related to this is presented in the context of advanced HIV and might not apply to those with CD4 counts ≥ 350 cells/μL and/or a suppressed HIV viral load.

In terms of HIV acquisition, syphilis causes transient immunosuppression and can weaken the host response to HIV, increasing the likelihood of exposure leading to HIV infection. In addition to this, chancres are particularly vulnerable, well vascularised sites for HIV to enter the bloodstream and establish primary infection(17, 18).

The impact of HIV on syphilis is explained by the immunodeficiency caused by HIV and the presentation of syphilis may be more severe or atypical, particularly in the severely immunosuppressed. These individuals are more likely to develop multiple, deeper or larger chancres and can have primary and secondary infection overlap(19). This trend continues in the context of neurosyphilis: A review of syphilis cases in Los Angeles between 2001 and 2004 showed a 2.1% incidence of neurosyphilis among those infected with HIV compared to 0.6% among those without HIV(20). The likelihood of developing neurosyphilis has been linked to the degree of immunosuppression caused by HIV with it being suggested that patients with a CD4 count of ≤ 350 cells/μL have a 3-fold increase in neurological involvement(21).

ASYMPTOMATIC NEUROSYPHILIS

Asymptomatic neurosyphilis is a topic of significant debate and scientific uncertainty. Concerns arose from studies which reported a greater level of neurocognitive impairment in HIV positive patients with previous early-syphilis but no diagnosis of neurosyphilis who were treated with standard Benzathine Penicillin G, which does not cross the blood-brain barrier, when compared to those without previous syphilis. Unfortunately these studies did not consider confounding factors such as alcohol consumption, smoking history, CD4 count, HIV viral load, recreational drug use and other co-infections(22, 23).

It is known that both pathogens can cause meningeal inflammation, leading to increased CSF penetration by the other infectious agent. Patients with concurrent HIV and syphilis infections have been found to have a higher CSF HIV viral load(17) which itself is known to be associated with neurocognitive impairment(17, 24). A recent prospective study found no association

between neurosyphilis and cognitive impairment in HIV positive individuals but did identify significantly higher levels of inflammatory markers that are associated with the development of cognitive impairment in the CSF of patients with neurosyphilis(25).

A study in the UK of 64 HIV positive patients with early syphilis that were treated with a single dose of Benzathine Penicillin G found that the risk of asymptomatic neurosyphilis was unlikely as only one patient developed asymptomatic neurosyphilis, as determined by CSF parameters(26). This contrasts with a study in the USA which found rates of asymptomatic neurosyphilis of 22% among 46 HIV positive, asymptomatic patients who underwent lumbar puncture(27). These differing rates of asymptomatic neurosyphilis likely reflect levels of immunosuppression, anti-retroviral therapy status, and severity of syphilis infection. The knowledge that syphilis causes neuro-inflammation in HIV infection, coupled with uncertainties surrounding the prevalence, clinical significance, and optimal treatment of asymptomatic neurosyphilis has left clinicians uncertain about whether all HIV positive patients should either undergo a lumbar puncture and/or be treated with a neuropenetrative antibiotic regimen.

DIAGNOSIS OF NEUROSYPHILIS

The presence of syphilis infection and neurological symptoms should raise significant suspicion of neurosyphilis. The following investigations must be interpreted with an understanding of their limitations and in the context of the clinical picture.

Microscopy

Genital syphilis can be diagnosed by swabbing a chancre and performing dark ground microscopy which will reveal the presence of *T. pallidum*(5). This technique is still used in genitourinary medicine clinics and can be used on samples obtained from biopsies, including in suspected cases of neurosyphilis.

Blood Tests

Syphilis can be difficult to diagnose due to the several weeks delay between exposure and seroconversion. When suspected, patients are screened with an enzyme linked immunosorbent assay (EIA) (Table 1). Other treponemes which affect humans include the endemic treponematoses bejel (*Treponema pallidum* subsp. *endemicum*) and yaws (*Treponema pallidum* subsp. *pertenue*) so a positive test will need to be taken in the context of the clinical picture and history(28). A confirmatory test called the *T. pallidum* haemagglutination (TPHA) or *T. pallidum* particle agglutination (TPPA) is then performed although in some settings this may be the only treponemal-specific test performed. EIA, TPHA and TPPA remain positive for life. In individuals with a positive TPHA/TPPA either a venereal disease research laboratory (VDRL) or reactive plasma reagin test (RPR) is carried out: these detect anti-cardiolipin antibodies in the blood and are given as a titer which is used to assess burden of infection, monitor response to treatment and diagnose treatment failure or re-infection(5, 28).

Table 1: How to interpret syphilis serology

	EIA IgG/IgM	TPPA or TPHA	VDRL or RPR
Never	-	-	-
Early	+	+	-
Secondary	+	+	+
Late	+	+	-
Treated	+	+	-
Reinfected	+	+	+
False Positive EIA	+	-	-
False Positive TPPA/TPHA	-	+	-
False Positive RPR	-	-	+

EIA: Enzyme-linked immunosorbent assay, RPR: Rapid plasma reagin, TPHA: Treponema pallidum haemagglutination, TPPA: Treponema pallidum particle agglutination, VDRL: Venereal disease research laboratory.

CSF Analysis

Diagnosis of neurosyphilis with CSF analysis is often difficult. CSF abnormalities include elevated white blood cell (WBC) count (with predominance of lymphocytes), elevated protein and a reactive CSF-VDRL or RPR. These CSF abnormalities must be taken in the context of the clinical findings (6, 29). Headache and visual disturbance have been strongly associated with symptomatic neurosyphilis in HIV positive individuals however, as described earlier, the manifestations are extremely variable and these symptoms are non-specific(9). Neurological symptoms and signs must be sought with extreme care in patients with syphilis and HIV co-infection and the possibility of asymptomatic neurosyphilis must be appreciated(30). In asymptomatic individuals diagnosis is based on CSF abnormalities alone and these may be less marked(9). Neurosyphilis may be the first presentation in a patient with HIV so all patients diagnosed with neurosyphilis should be tested for HIV.

Several clinical and laboratory parameters are used to aid the diagnosis of neurosyphilis in the context of HIV and are of use when deciding which patients should undergo CSF examination and receive enhanced treatment with a neuropenetrative regimen (Tables 2 and 3). There is consensus that in the presence of neurological symptoms such as headache or altered mental state a CSF analysis should be performed regardless of laboratory parameters. Indications for CSF analysis in patients who are asymptomatic however, have been debated. European and Canadian guidelines state that patients with a CD4 count of ≤350 cells/μL or a VDRL/RPR titer of ≥1:32 should undergo lumbar puncture although this differs from the CDC recommendation (31, 32). *Ghanem et al* found these criteria to be most reliable in identifying asymptomatic neurosyphilis(27). The lack of systematic research into this area contributes to a lack of consensus on which patients will benefit from screening and enhanced treatment for neurosyphilis.

Table 2: Indications for a lumbar puncture

Neurological signs
Ocular involvement
CD4 count <350 cells/μL*
VDRL/RPR titer ≥1:32*
ART naïve*

* consider

Table 3: Factors suggesting a diagnosis of neurosyphilis:

Neurological signs
Ocular involvement
Positive CSF test including: VDRL, RPR, TPHA, TPPA, PCR
CSF pleocytosis: >20 cells if ART naïve, >10 cells if ART exposed

ART: Antiretroviral therapy, CSF: cerebrospinal fluid, PCR: Polymerase chain reaction, RPR: Rapid plasma reagin, TPHA: Treponema pallidum haemagglutination, TPPA: Treponema pallidum particle agglutination, VDRL: Venereal disease research laboratory.

The CSF-VDRL is the 'gold standard' in terms of specificity for neurosyphilis but has significant limitations: Its variable sensitivity (30%-70%) means a non-reactive CSF-VDRL does not exclude the diagnosis of neurosyphilis. However as CSF-VDRL is highly specific a reactive CSF-VDRL confirms the diagnosis(33). CSF-RPR is easier to perform but has lower sensitivity than VDRL(34). CSF treponemal tests such as the TPPA can be used in conjunction with VDRL as they are highly sensitive but non-specific therefore a negative treponemal test excludes the diagnosis of neurosyphilis. Some studies suggest high-titer CSF TPPA results are more specific for neurosyphilis(6, 33). CSF polymerase chain reaction (PCR), although not widely available, has sensitivity of 70-76% and a specificity of 87-92%(35).

Even in centres where each of these tests is available the results can often be inconclusive and the diagnosis may be made on CSF pleocytosis alone. Challenges arise here as HIV itself can cause CSF pleocytosis(9). Patients with neurosyphilis generally have a CSF WBC count >10 cells/μL however if a HIV positive patient has positive syphilis serology and a non-reactive CSF-VDRL a cut off of >20 cells/μL is often used(29). Clinicians need to be cautious when deciding an appropriate cut off as patients on ART and/or with an undetectable plasma HIV viral load are less likely to have CSF pleocytosis and therefore the lower cut off of >10 cells/μL might still be appropriate in this group. It is however still unclear as to whether the pleocytosis is due to syphilis, HIV, a combination of both or an alternative diagnosis so CSF pleocytosis is a poor diagnostic tool for neurosyphilis(29). A raised protein >0.45g/l may also suggest neurosyphilis but again lacks specificity(36).

This lack of an ideal diagnostic test has prompted research into new CSF diagnostic markers. The B lymphocyte chemoattractant chemokine CXCL13 has proven to be the most promising and could be used independent of CSF pleocytosis and CSF-VDRL(37). Levels decline after treatment so CXCL13 could potentially also be used as a marker of treatment response(38). If CXCL13 is to be used in clinical practice its sensitivity and specificity needs to be established and recommended cut off parameters identified(38).

NEUROIMAGING

Imaging can sometimes be helpful in the diagnosis and monitoring of neurosyphilis, although there are no abnormalities which are specific for the condition and scans can be normal. Owing to the meningovascular inflammation predominantly involving small to medium-sized vessels, areas of infarction or haemorrhage are perhaps most commonly observed, and often said to be within the middle cerebral and basilar artery territories, along with meningeal enhancement, non-specific white matter lesions and mild generalized atrophy (Figures 2 and 3)(39,40). scan can Magnetic Resonance Imaging (MRI) is preferred over Computed tomography (CT) given the superior parenchymal resolution and characterization of potential posterior fossa or spinal cord involvement. CT, MRI or even formal catheter angiography may be indicated to demonstrate vessel narrowing or irregularity particularly when alternative diagnoses such as non-infectious cerebral vasculitides are suspected(39, 41).

DIFFERENTIAL DIAGNOSIS

Neurosyphilis should be a differential diagnosis for any HIV positive patient presenting with unexplained neurological symptoms as listed in Table 4(11). Challenges arise due to the overlap of neurological manifestations caused by both organisms and the numerous pathologies which can be seen in advanced HIV infection. Either organism can independently cause acute or chronic meningitis, vasculitis, cranial neuropathies, cognitive decline, myelopathy and peripheral neuropathies(42). All HIV positive patients with neurological symptoms, including cognitive impairment, should be subject to an appropriate diagnostic workup to rule out common viral infections (particularly herpes simplex, varicella zoster, enterovirus), cryptococcal meningitis, tuberculosis, toxoplasmosis, lymphoma, progressive multifocal leucoencephalopathy and a detectable HIV viral load causing HIV encephalitis(13).

Table 4: Potential manifestations of Neurosyphilis

(Aseptic) meningitis
Chronic headache
Psychiatric illness
Cognitive impairment
Ischaemic stroke
Seizures
Mass lesion
Cranial (poly)neuropathy
Optic neuritis/optic atrophy
Ataxia
Transverse myelitis
Myelopathy
(Poly)radiculopathy
Peripheral neuropathy

TREATMENT

Penicillins remain the treatment of choice for all stages of syphilis with no penicillin resistance described. Guidelines currently recommend that, in the absence of central nervous system involvement, early (primary, secondary, and early latent) syphilis should be treated with a single dose of Benzathine Penicillin G (BPG) 2.4 million units (MU) intramuscularly (IM) and late latent syphilis should be treated with 3 doses BPG 2.4 MU IM at 1 week intervals, regardless of HIV status (Table 5) (6). Although this is the first-line recommended regimen a large review found that in HIV positive patients it is associated with serological failure (defined as a less than four-fold decline in RPR/VDRL titer) in between 0 and 33% of cases. This risk is reduced by roughly 60% with the use of antiretroviral therapy(17).

Table 5: Treatment regimen options for different stages of syphilis:

Early disease (<2yrs, primary, secondary, early latent)	a) BPG 2.4 MU IM stat b) Doxycycline 100mg BD for 14 days
Late latent disease (>2yrs) Tertiary, cardiovascular or gummatous	a) BPG 2.4 MU IM, 3 doses at weekly intervals b) Doxycycline 100mg PO BD for 28 days c) Amoxicillin 500mg PO QDS plus Probenecid 500mg PO QDS for 28 days
Neurosyphilis	a) Procaine penicillin 2.4 MU IM plus Probenecid 500mg PO QDS for 10-14 days b) Benzylpenicillin 10.8-14.4g daily given as 1.8-2.4g IV every 4 hours for 10-14 days c) Doxycycline 200mg PO BD for 28 days

	d) Amoxicillin 2g PO TDS plus Probenecid 500mg PO QDS for 28 days e) Ceftriaxone 2g IM or IV OD for 10-14 days

BD: Twice daily, BPG: Benzathine Penicillin G, IM: Intramuscular, IV: Intravenous, OD: Once daily, PO: Oral, TDS: Three times daily, QDS: Four times daily.

In patients for whom the diagnosis of neurosyphilis is established, treatment success is dependent upon patients reaching sustained treponemicidal penicillin levels in the CSF. To ensure CSF penetration, neurosyphilis is treated with an intensified regimen of 1-8-2.4 MU procaine penicillin given intramuscularly once daily for 10-14 days with oral probenecid 500mg four times a day. Alternatively, inpatient treatment can be given with benzyl penicillin 10.8-14.4g in total daily dose, given as 1.8-2.4g intravenously every 4 hours for 10-14 days to those who are acutely unwell(6). In our centre in Brighton all co-infected patients are treated with procaine penicillin regardless of whether either a lumbar puncture has been performed or neurosyphilis diagnosis has been confirmed because of the concern of asymptomatic neurosyphilis. At this site, Warwick et al. reported high serological treatment success rates at 98% at 6 months as well as good patient adherence despite the prolonged course of intramuscular treatment(43). A global shortage of probenecid however makes it unfeasible to presumptively treat patients for neurosyphilis without CSF analysis.

If a patient with neurosyphilis has significant penicillin allergy, penicillin desensitisation is thought to be the best option(31, 32, 44). When penicillin based regimens are not available doxycycline 200mg twice per day for 28 days is recommended(6). Due to its tolerability and resistance concerns erythromycin and azithromycin are no longer recommended particularly in men who have sex with men where syphilis is highly prevalent(45). A small observational study reported that ceftriaxone 1 to 2g per day intramuscularly for 10 days is an effective alternative to penicillin however evidence is limited(46). High dose oral amoxicillin plus oral probenecid has also proven to be highly effective in a retrospective observational study of patients with early and late syphilis and HIV infection (47).

Steroids and the Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute pyrexial illness with associated headaches, myalgia and rigors which is commonly experienced by patients several hours after initiating treatment. This is a pro-inflammatory response caused by the destruction of large volumes of treponemes and is seen particularly among those with high VDRL/RPR titers. Guidelines recommend that patients with neurosyphilis be prescribed three days of oral prednisolone 40mg: 24 hours before and 48 hours after commencing syphilis treatment(48). Although data is limited it appears that steroids do not reduce the incidence of the reaction but may reduce the severity(6). Given that steroids have little or no effect on symptomatic neurological sequelae and are known to cause immunosuppression it is safer not to prescribe them to

immunosuppressed patients. The only caveat to this is in cases of ocular syphilis where worsening of symptoms, which may not be reversible, can be caused by a Jarisch-Herxheimer reaction and therefore the prescription of steroids should be considered. In cases of advanced immunosuppression seek guidance from a HIV specialist when considering prescribing steroids.

OCULAR SYPHILIS

Syphilis can affect the eyes in a multitude of ways. Conceivably the most well remembered ocular manifestation is the Argyll Robertson pupils which accommodate but do not react to light and thus demonstrate light-near dissociation. This finding is highly specific for syphilis but can also be seen in diabetic neuropathy or as part of a dorsal midbrain syndrome. Anterior or posterior uveitis is perhaps most commonly encountered but papillary conjunctivitis, scleritis, neuroretinitis and retinal vasculitis are also observed, usually in secondary and tertiary stages. Furthermore, syphilis is on the important list of differential diagnoses for presentations of progressive optic neuropathy, and thus should be excluded in patients whose optic neuritis is ‘atypical’. Ocular syphilis is considered to be a type of neurosyphilis, although it is not always accompanied by syphilitic meningitis or abnormal CSF results. However, given that the recommended treatment is the same neuropenetrative regimen used for neurosyphilis(48), it may not be necessary to perform CSF analysis in every case.

MONITORING

Patients who have been treated for neurosyphilis should have their blood RPR/VDRL titers monitored on a three-monthly basis with serological response defined as a four-fold decline in titer or reversion to a seronegative state(6). Patients with HIV may demonstrate a slower time to serological response of up to 12 months due to loss of immune function such that there is a low-level production of antibodies. In patients with serological failure - a less than four-fold decline in titer, static titer or increase in titer - a thorough history and examination should be conducted to determine whether this could be due to treatment failure or re-infection. It may be necessary to perform repeat CSF analysis in this situation(49).

Repeat lumbar puncture should also be performed if significant CSF pleocytosis (>10 cells/μL) or positive CSF-VDRL were present at initial CSF examination. CSF examination should be repeated at least six-monthly until the cell count is normal but may be necessary more frequently depending on the clinical picture. Repeat CSF examination may also demonstrate reduction in the CSF-VDRL concentration as a result of treatment, but these changes occur slowly and persistent abnormalities may not necessarily suggest treatment failure. If a pleocytosis persists after six months, without alternative explanation, re-treatment is advised(50).

FUTURE RESEARCH

Further research is required to determine to what extent previous or ongoing syphilis infection in people living with HIV contributes to neurocognitive decline and which patients with HIV and syphilis co-infection should be actively investigated for neurosyphilis. Comparison of serological and clinical outcomes of patients with HIV and early syphilis treated with single-dose Benzathine Penicillin G compared to the neuropenetrative procaine penicillin regimen is needed. More research is also required to validate improved diagnostic markers such as CXCL13.

Case One:

A 42 year old HIV positive man presents to a sexual health clinic with a primary chancre and evidence of *T.pallidum* on dark ground microscopy. His most recent CD4 count is 55 cells/μL and he is not on antiretroviral therapy. Neurological examination including fundoscopy is normal.

This man should certainly be offered a lumbar puncture. He is at high risk of neurosyphilis as well as other opportunistic infections that can cause meningoencephalitis. If the lumbar puncture identifies WBC <10 cells/μL and a negative CSF-VDRL then you can be confident he does not have neurosyphilis. If he refuses a lumbar puncture then commence outpatient treatment with a neuropenetrative regimen such as procaine penicillin with probenecid for 14 days or doxycycline for 28 days. It is not advisable to give steroids to someone with this level of immunosuppression.

Case Two:

A 26 year old HIV positive man presents with a 24 hour history of fever, headache and neck stiffness. He is on antiretroviral therapy, his most recent CD4 was 550 cells/μL and he reports having attended a sex party four weeks ago. Syphilis serology identifies positive EIA and TPHA but negative VDRL. Lumbar puncture reveals WBC of 12 cells/μL, predominantly lymphocytes, and CSF VDRL is negative.

The bloods suggest either primary syphilis or a previously treated infection. Correlating this with previous serology and a good history should help to establish which. If primary syphilis is likely then this event signifies neuroinvasion of T.pallidum which is often cleared spontaneously by patients but given the symptoms and pleocytosis he should be treated with a neuropenetrative penicillin regimen. If this is not a case of primary syphilis then other causes of his symptoms and pleocytosis, such as a viral meningitis, should be sought.

Case Three:

A 60 year old HIV positive man with a CD4 count of 623 cells/μL and on effective antiretroviral therapy presents to a specialist HIV and neurology clinic with a history of cognitive decline. His bloods reveal a positive EIA and TPHA but negative VDRL. He does not recall receiving treatment for syphilis in the past. His MRI shows generalized atrophy.

Lumbar puncture identified WBC of 8 cells/μL and all other tests including CSF-VDRL are negative.

This man has certainly had syphilis in the past and he may well have been treated without remembering. However, his bloods may indicate late-latent infection which may be the cause of his cognitive impairment. A negative CSF-VDRL does not rule out this diagnosis and he should be treated for neurosyphilis whilst continuing other investigations for his cognitive decline.

KEY POINTS FOR NEUROLOGISTS

1. Always consider syphilis in the differential diagnosis of neurological presentations in HIV positive individuals.
2. In HIV positive individuals with serological evidence of syphilis always take a detailed history and examine for neurological signs.
3. Lumbar puncture should be considered in all patients with HIV and syphilis co-infection with neurological signs or if the CD4 count is <350 cells/μL, serum RPR/VDRL titer is ≥1:32, or they are not on antiretroviral therapy.
4. If CSF-VDRL is negative, still consider neurosyphilis in patients with neurological signs and/or a CSF WBC >10 cells/μL in treated HIV infection or >20 cells/μL in untreated infection.
5. Always perform a HIV test if a patient who is diagnosed with neurosyphilis is not known to be HIV positive.

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Figures Legend

Figure 1: Number of syphilis infections in England between 2007 and 2016(4)

Figure 2: MRI T2 signal alteration in the right cerebral peduncle (arrowed) of a patient with meningovascular neurosyphilis(40).

Figure 3: Cerebral infarction in a 22-year old HIV- positive patient with neurosyphilis. T1-weighted image with gadolinium(40).

References

1. Soloman MM, Mayer KH. Evolution of the syphilis epidemic among men who have sex with men. Sex Health. 2015;12(2):96-102.
2. England PH. Syphilis epidemiology in London: sustained high number of cases in men who have sex with men. London: PHE publications; 2016 Aug. p. 1-27.
3. CFDCA. Sexually Transmitted Disease Surveillance 2015. In: Services USDoHaH, editor. Atlanta: CDC; 2016. p. 1-176.
4. England PH. Sexually transmitted infections and chlamydia screening in England, 2016. In: report Hp, editor. 2016 Jun. p. 1-20.
5. Mattei PL, Beachkofsky TM , Gilson RT, Wisco OJ. Syphilis: a reemerging infection. Am Fam Physician. 2012;86(5):433-40.
6. Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C, et al. UK national guidelines on the management of syphilis 2015. International Journal of STD & AIDS. 2015;27(6):421-46.
7. Marra CM. Update on neurosyphilis. Current Infectious Disease Reports. 2009;11(2):127-34.
8. Marra CM, Gary DW, Kuypers J, Jacobson MA. Diagnosis of neurosyphilis in patients infected with human immunodeficiency virus type 1. J Infect Dis. 1996;174:219-21.
9. Ho EL, Spudich SS. Neurosyphilis and the impact of HIV infection. Sexual Health. 2015;12(2):148-54.
10. Tramont EC. 'Treponema pallidum' (Syphilis). 6th ed. Philadelphia: Churchill Livingstone; 2005.
11. Chahine LM, Khoriaty RN, Tomford WJ, Hussain MS. The changing face of neurosyphilis. Int J Stroke. 2011;6(2):136-43.
12. Harris DE, Enterline DS, Tien RD. Neurosyphilis in patients with AIDS. Neuroimaging Clin N Am. 1997;7(2):215-21.
13. Musher DM. Syphilis, neurosyphilis, penicillin, and AIDS. J Infect Dis. 1991;163(6):1201-6.
14. Lanska MJ, Lanska DJ, Schmidley JW. Syphilitic polyradiculopathy in an HIV-positive man. Neurology. 1988;38(8):1297-301.
15. Chesson HW, Heffelfinger JD, Voigt RF, Collins D. Estimates of primary and secondary syphilis rates in persons with HIV in the United States, 2002. Sex Transm Dis. 2005;32(5):265-9.
16. Golden MR, Marra CM, Holmes KK. Update on syphilis: Resurgence of an old problem. JAMA. 2003;290(11):1510-4.
17. Ghanem KG. Evaluation and Management of Syphilis in the HIV-Infected Patient. Curr Infect Dis Rep. 2010;12(2):140-6.
18. Arora PN, Sastry CV. HIV infection and genital ulcer disease. Indian J Sex Transm Dis. 1992;13(2):71-3.

19. Zetola NM, Klausner JD. Syphilis and HIV infection: an update. Clin Infect Dis. 2007;44(9):1222-8.
20. Taylor MM, Aynalem G, Olea LM, He P, Smith LV, Kerndt PR. A consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001-2004. Sex Transm Dis. 2008;35(5):430-4.
21. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. Aids. 2008;22(10):1145-51.
22. Vera J, Garvy L, Tipple C, Goldmeirer D, Winston A. A past history of syphilis is associated with poorer performance in the cognitive domains of memory and learning in HIVinfected subjects on stable cART. HIV Med. 2012;13:51.
23. Marra CM, Deutsch R, Collier AC, Morgello S, Letendre S, Clifford D, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. International journal of STD & AIDS. 2013;24(5):351-5.
24. Robertson K, Fiscus S, Kapoor C, Robertson W, Schneider G, Shepard R, et al. CSF, plasma viral load and HIV associated dementia. Journal of neurovirology. 1998;4(1):90-4.
25. Ho EL, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC, Lukehart SA, et al. Neurosyphilis Increases Human Immunodeficiency Virus (HIV)-associated Central Nervous System Inflammation but Does Not Explain Cognitive Impairment in HIV-infected Individuals With Syphilis. Clinical Infectious Diseases. 2017;65(6):943-8.
26. Tomkins A, Ahmad S, Cousins DE, Vilar FJ, Higgins SP. O32 Asymptomatic neurosyphilis is unlikely in hiv infected patients after treatment for early syphilis with benzathine penicillin g. Sexually Transmitted Infections. 2015;91(Suppl 1):A11.
27. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. Clin Infect Dis. 2009;48(6):816-21.
28. Lafond RE, Lukehart SA. Biological basis for syphilis. Clin Microbiol Rev. 2006;19.
29. Marra CM, Maxwell CL, Collier AC, Robertson KR, Imrie A. Interpreting cerebrospinal fluid pleocytosis in HIV in the era of potent antiretroviral therapy. BMC Infectious Diseases. 2007;7(1):37.
30. Tipple C. Impact of HIV-1 infection on the clinical presentation of syphilis in men who have sex with men. Sexual Health. 2015;12(2):110-8.
31. Canada PHAo. Canadian guidelines on sexually transmitted infections 2013.
32. Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potocnik M, et al. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014;28(12):1581-93.
33. Castro R, Prieto ES, Aguas MJ, Manata MJ, Botas J, Araujo C, et al. Evaluation of the Treponema pallidum particle agglutination technique (TP.PA) in the diagnosis of neurosyphilis. J Clin Lab Anal. 2006;20(6):233-8.
34. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis. 2012;39(6):453-7.
35. Castro R, Aguas MJ, Batista T, Araujo C, Mansinho K, Pereira Fda L. Detection of Treponema pallidum Sp. Pallidum DNA in Cerebrospinal Fluid (CSF) by Two PCR Techniques. J Clin Lab Anal. 2016;30(5):628-32.

36. Timmermans M, Carr J. Neurosyphilis in the modern era. J Neurol Neurosurg Psychiatry. 2004;75(12):1727-30.
37. Marra CM, Tantalo LC, Sahi SK, Maxwell CL, Lukehart SA. CXCL13 as a Cerebrospinal Fluid Marker for Neurosyphilis in HIV-infected Patients with Syphilis. Sexually transmitted diseases. 2010;37(5):283-7.
38. Hu R, Lu C, Lu S, Hu Y, Ma H, Lai W, et al. Value of CXCL13 in diagnosing asymptomatic neurosyphilis in HIV-infected patients. International Journal of STD & AIDS. 2015;27(2):141-6.
39. Khamaysi Z, Bergman R, Telman G, Goldsher D. Clinical and imaging findings in patients with neurosyphilis: a study of a cohort and review of the literature. Int J Dermatol. 2014;53(7):812-9.
40. Carr J. Neurosyphilis. Practical Neurology. 2003;3(6):328.
41. Czarnowska-Cubala M, Wiglusz MS, Cubala WJ, Jakuszkowiak-Wojten K, Landowski J, Krysta K. MR findings in neurosyphilis--a literature review with a focus on a practical approach to neuroimaging. Psychiatr Danub. 2013;25 Suppl 2:S153-7.
42. Berger JR. Neurosyphilis in human immunodeficiency virus type 1-seropositive individuals. A prospective study. Arch Neurol. 1991;48(7):700-2.
43. Warwick Z, Dean G, Fisher M. Should syphilis be treated differently in HIV-positive and HIV-negative individuals? Treatment outcomes at a university hospital, Brighton, UK. Int J STD AIDS. 2009;20(4):229-30.
44. Worwoski KA,Bolan GA. Sexually transmitted diseases treatment guidelines 2015. CDC Recommendations and reports. 2015;64(3):1-135.
45. Lukehart SA, Godornes C, Molini BJ, Sonnett P, Hopkins S, Mulcahy F, et al. Macrolide Resistance in Treponema pallidum in the United States and Ireland. New England Journal of Medicine. 2004;351(2):154-8.
46. Smith NH, Musher DM, Huang DB, Rodriguez PS, Dowell ME, Ace W, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD AIDS. 2004;15(5):328-32.
47. Tanizaki R, Nishijima T, Aoki T, Teruya K, Kikuchi Y, Oka S, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis. 2015;61(2):177-83.
48. Gudjonsson H, Skog E. The effect of prednisolone on the Jarisch-Herxheimer reaction. Acta Derm Venereol. 1968;48(1):15-8.
49. Marra CM, Maxwell CL, Tantalo L, Eaton M, Rompalo AM, Raines C, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis. 2004;38(7):1001-6.
50. Ghanem KG, Workowski KA. Management of adult syphilis. Clin Infect Dis. 2011;53 Suppl 3:S110-28.