Neurosyphilis: A Current Review

Judith A. O'Donnell, MD, and Christopher L. Emery, MD*

Address
*Division of Infectious Diseases, Room 6303, NCB Mailstop 461, Hahnemann University Hospital, Broad and Vine Streets, Philadelphia, PA 19102, USA.
E-mail: jodonne@drexelmed.edu

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Neurosyphilis continues to be a difficult diagnosis for clinicians. The decision to perform a lumbar puncture, interpretation of cerebrospinal fluid findings, clear diagnostic guidelines, establishment of definitive therapy (including alternatives to penicillins), and approach to the follow-up of patients with neurosyphilis are all areas that pose ongoing challenges to clinicians. Coinfection with HIV has also further complicated the already challenging arena of neurosyphilis presentation, diagnosis, and management. Clinicians must recognize the recent changes in the epidemiology of syphilis and know when to initiate appropriate screening. This article highlights the limitations and controversies related to neurosyphilis diagnosis and treatment, and current recommendations on management of patients with neurosyphilis, including those coinfected with HIV.

Introduction

Central nervous system (CNS) infection with *Treponema pallidum*, the causative agent of syphilis, has been a vexing disease for physicians for centuries. In the pre-antibiotic era, patients were often subjected to serial lumbar punctures to assess the therapeutic effectiveness of arsenicals, in an attempt to cure the infection and halt the progression of CNS disease [1]. Arsenicals, and all other therapies used before the discovery of penicillin, failed to eradicate *T. pallidum*. With the widespread use of penicillin therapy after World War II, syphilis rates in the United States decreased dramatically for several decades [2]. Despite the success of penicillin therapy, certain clinical aspects of syphilis, and neurosyphilis in particular, have remained problematic in the management of this disease. The decision to perform a lumbar puncture, the interpretation of cerebrospinal fluid (CSF) findings, clear diagnostic guidelines for neurosyphilis, establishment of definitive therapy (including alternatives to penicillins), and approach to the follow-up of patients with neurosyphilis are fraught with uncertainty. With the advent of HIV infection in the early 1980s, a resurgence of syphilis was seen in the United States, and many early reports in the 1980s and early 1990s suggested a more rapid progression of infection with *T. pallidum* to CNS disease in this patient population [3–6]. The potential synergistic effect of HIV infection on syphilis further complicated the already challenging arena of neurosyphilis presentation, diagnosis, and management. This article highlights the recent changes in the epidemiology of syphilis, the limitations and controversies related to neurosyphilis diagnosis and treatment, and provides current recommendations on management of patients with neurosyphilis, including those coinfected with HIV.

Changing Epidemiology of Syphilis

With the introduction of penicillin as an effective therapy for syphilis, primary and secondary syphilis case rates decreased dramatically through the latter half of the 20th century in the United States [2]. Neurosyphilis, once so common it was estimated to account for 10% to 20% of asylum admissions in the pre-antibiotic era, also became a rare diagnosis [7]. Although syphilis rates have continued to decrease among women and infants from 2000 to 2003, overall case rates began to increase again in 2000 [2]. Syphilis in the United States is currently most commonly seen in specific geographic regions (the southeast) and more commonly affects blacks, those infected with HIV, and men who have sex with men (MSM) [2]. Many US cities have identified syphilis outbreaks in MSM, and between 20% to 73% of those diagnosed have also been infected with HIV [8–10]. The increased rates of syphilis and other sexually transmitted diseases (STDs) in MSM are multifactorial. Lack of knowledge regarding risk of acquisition of STDs with certain sexual practices such as oral sex, relaxed attitude toward safer sex practices among younger MSM, and misconceptions about need for condom use when both partners are HIV-infected have likely contributed to increased STD rates in this population [8,10]. At present, it is not known how many of those infected in recent syphilis outbreaks may go on to develop late manifestations of syphilis, particularly neurosyphilis, because neurosyphilis case rates are not regularly tracked and reported by the US Centers for Disease Control and Prevention (CDC). In 2005, it is most important that clinicians recognize the increased rates of syphilis in MSM and have an enhanced suspicion for disease and screen appropriately.

Clinical Manifestations of Neurosyphilis

Treponema pallidum invades the CNS relatively early in infection, seeding the meninges during the primary, or more

commonly, secondary stage of disease [11]. Spinal fluid abnormalities are commonly identified when patients with primary or secondary syphilis and no signs or symptoms of CNS disease undergo CSF examination. It has been estimated that between 30% and 50% of such patients may have some abnormality on CSF examination [1,11,12•]. At most, 1% to 5% of these patients will develop symptomatic disease, such as aseptic meningitis, during the secondary syphilis stage [12•,13]. Despite the frequency of CNS invasion and abnormalities of CSF, most patients will clear their CNS infection even without therapy, as was noted in the pre-antibiotic era [1,12•,13]. Those who fail to clear *T. pallidum* from the CNS are at risk for neurosyphilis. An estimated one in 250 patients may eventually develop late manifestations of neurosyphilis [14].

Neurosyphilis can occur during the secondary stage (early neurosyphilis) and tertiary stage (late neurosyphilis) of disease. Table 1 outlines the many clinical manifestations of neurosyphilis. Early neurosyphilis can manifest as early as the primary or secondary stage or within 2 to 5 years of infection. Early neurosyphilis affects the meninges, cerebral vasculature and CSF, and most often presents as aseptic meningitis during secondary syphilis. When neurosyphilis manifests as aseptic meningitis, the CSF is always abnormal. CSF findings include an increased opening pressure, increased protein, a CSF white blood cell (WBC) count between 2 and 200 cells with a mononuclear predominance, and hypoglycorrhachia in 40% of cases [1,11,13]. The CSF Venereal Disease Research Laboratory (VDRL) has a diagnostic sensitivity of 30% to 70% but is highly specific. Early neurosyphilis may also present as eye disease such as uveitis, or less commonly with acute hydrocephalus or cranial nerve involvement [1]. Cranial nerves II, III, VI, and VII are those most commonly affected, as determined in pre-antibioitc era studies [1]. Early neurosyphilis may also present as seizure, and syphilis should be ruled out in patients who present with status epilepticus and have other risk factors for syphilis [14,15]. Early CNS syphilis infection may rarely manifest in the spinal cord; in these cases, the patient may have myelitis or meningomyelitis [16].

Late neurosyphilis may affect the cerebral vasculature, or brain or spinal cord parenchyma. Late neurosyphilis can manifest within 2 to 30 years after initial infection. Clinical presentations include meningovascular syphilis presenting as stroke; parenchymatous syphilis presenting as progressive personality changes, leading to psychiatric or dementing illness; or tabes dorsalis. Some authorities categorize meningovascular syphilis, which presents as stroke, as an early neurosyphilis manifestation, because meningovascular neurosyphilis commonly presents within the first 5 years after infection [12•].

Syphilitic eye disease may also occur early or late in the course of infection. Early eye disease can manifest as iritis or uveitis. Pathogenesis of early eye disease is thought to be secondary to deposition of circulating immune complexes, and the CSF, when examined, is most often normal [13]. Late-stage syphilis infection of the eye can present as optic neuritis or optic atrophy. Afflicted patients usually present with progressive visual loss, usually in one eye at a time [1,13]. Whenever the eye is involved, the patient is considered to have neurosyphilis and managed accordingly. Treatment with penicillin will avert further visual loss in these patients [13]. Syphilitic otitis is a more nebulous entity. It is thought to occur when the otic branch of cranial nerve VIII is involved in infection; sudden onset (over a period of weeks) of hearing loss is the usual presentation [14,17]. The hearing loss is sensorineural and often unilateral. Sensorineural deafness has been attributed to syphilis infection, particularly when other causes have been excluded and there is positive serologic evidence of syphilis infection [17]. CSF examination is usually normal in these patients [17]. Syphilitic otitis is also considered a form of neurosyphilis.

Although it is a widely accepted belief that most individuals with early CNS invasion/infection with *T. pallidum* will clear the CNS component of the infection even without therapy targeted to achieve treponemicidal concentrations in the CSF, it is less clear what happens in those who are immunosuppressed. During the early HIV epidemic, there were numerous case reports that suggested HIV coinfection may alter the clinical presentation and natural history of syphilis infection [4,5]. Specifically, reports described rapid progression to tertiary disease, including neurosyphilis, and treatment failures or relapsing disease [3,6]. In the largest prospective early syphilis therapy trial preformed to date, 101 of the 541 enrolled patients were also HIV-infected, and several important findings were reported regarding those coinfected with syphilis and HIV infection [18••]. Such patients were more likely to have a higher rapid plasma reagin (RPR) titer at presentation, multiple chancres and delayed healing of chancres, CSF abnormalities when spinal fluid examination was performed, and serologic treatment failure [18••,19•]. Likelihood of CNS invasion with *T. pallidum* was not significantly different between HIV-infected and -uninfected patients in this study. Additionally, there was only one clinical treatment failure, which occurred in an HIV-infected individual. The HIV-infected patients responded equally well to standard therapy for early syphilis, and no unusual complications or rapid progression of disease were identified. However, patients in this study were only followed for 12 months after diagnosis, so long-term follow-up and progression to neurosyphilis cannot be reliably ascertained in this study population.

When Should Neurosyphilis Be Considered?

Clinicians should consider the diagnosis of neurosyphilis when any of the clinical manifestations noted in Table 1 are present. A spinal fluid examination should be performed in all such patients. The CDC also recommends lumbar puncture in patients who have active tertiary syphilis elsewhere (gummatous disease or aortitis), in those who are HIV-infected with late latent syphilis, or in

Table 1. Clinical manifestations of neurosyphilis [1,23]

Manifestations	Timing after infection	Pathophysiology	Clinical presentation
Asymptomatic	Early or late	—	No signs or symptoms; CSF is abnormal
Aseptic meningitis	Early (usually in first 1–4 years)	Inflammation of meninges	Headache, neck stiffness, fevers, meningeal signs; CSF is always abnormal (see text)
Uveitis (anterior > posterior; panuveitis)	Early or late	Deposition of circulating immune complexes in early disease	Blurred vision, red eye, floaters, and pain may all be present; no pathognomonic signs on examination; CSF may be normal
Meningovascular	Late (some experts categorize it as early because it usually occurs within 2–7 years after infection)	Focal arteritis, usually smaller vessels with thrombosis and infarction plus meningeal inflammation	Stroke; deficits most common in middle cerebral artery distribution; rarely involves spinal cord vessels; CSF is abnormal with increased WBC count and protein and positive VDRL-CSF in most patients
Parenchymatous: general paresis (general paralysis of the insane, dementia paralytica)	Late (10–20 years)	Progressive neuronal loss in cerebral cortex; diffuse cortical atrophy most prominent in frontal and temporal lobes	Deterioration of cognitive function and concentration, irritability, memory loss, personality changes, depression, psychosis, and eventual dementia; seizures and hemiparesis, aphasia, and incontinence are late manifestations
Parenchymatous: tabes dorsalis	Late (15–25 years)	Leptomeningeal inflammation of dorsal nerve roots; results in atrophy of posterior columns of spinal cord and posterior nerve roots	Lancinating "lightning pains" in legs, paresthesias, loss of proprioception, decreased DTRs, progressive ataxia, bowel and bladder incontinence; Argyll Robertson pupil in approximately 50% of patients; CSF may be normal
Optic neuritis/ optic atrophy	Late	—	Progressive visual loss, one eye at a time
Otitis	Early or late	Involvement of cranial nerve VIII	Sudden onset of hearing loss, progressive over a few weeks; often unilateral; must rule out other causes of sensorineural deafness

CSF—cerebrospinal fluid; DTR—deep tendon reflex; VDRL—Venereal Disease Research Laboratory; WBC—white blood cell.

patients with other stages of syphilis who have serologic treatment failure after an appropriate duration of follow-up [20••]. Additionally, some experts believe patients with late latent syphilis in whom the RPR titer is 1:32 or higher may also warrant CSF examination [20••].

Controversy continues to exist regarding the need for a lumbar puncture in patients with syphilis and HIV infection. Some experts recommend that all patients with HIV and syphilis, regardless of stage, undergo CSF examination [14,20••]. Rationale for this practice is borne out of several issues regarding the natural history, diagnosis, and treatment of syphilis. First, many clinicians continue to be concerned about potential rapid progression to neurosyphilis in HIV-infected patients. Although the findings from the large prospective treatment trial of early syphilis (see earlier text) did not support this phenomenon, recent data suggest this concern may have credence, at least in a certain subset of coinfected patients [18••]. In a study published in 2004 that examined 326 patients with known syphilis and no diagnosis of neurosyphilis who met criteria for lumbar puncture, several interesting findings were reported [21•]. First, 65 of the patients had neurosyphilis as defined as a CSF WBC count greater than 20 cells per μL or a reactive VDRL-CSF. Second, in multivariate analyses, the serum RPR titer of 1:32 or greater increased the odds of neurosyphilis in HIV-coinfected patients by more than 10-fold. In the same study, a CD4 cell count of 350 cells per μL or less also increased the odds of neurosyphilis by 3.1-fold. Although this study's findings have not yet been replicated, they suggest that in certain subsets of HIV-infected patients with non-neurologic syphilis, specifically those with an RPR of 1:32 or greater or a CD4 count less than 350 cells per μL, there may be a need for lumbar puncture.

A second reason cited to support the recommendation to perform lumbar puncture in all patients with HIV and syphilis infection is that benzathine penicillin G (BPG), the standard therapy for primary, secondary, and latent syphilis infection, does not achieve treponemicidal concentrations within the CNS [22]. Most experts think that treponemicidal drug concentrations are not necessary for the overwhelming majority of infected patients, because *T. pallidum* is most commonly cleared by the host from the

Table 2. Criteria for diagnosis of neurosyphilis [20••]

CNS or ophthalmic signs or symptoms, plus
Serologic evidence (positive nontreponemal and treponemal test results) for syphilis infection
Plus one of the following:
Positive VDRL-CSF
Increased CSF protein (> 40 mg/dL)
Increased CSF WBC count (> 5 mononuclear cells/μL)

CNS—central nervous system; CSF—cerebrospinal fluid; VDRL—Venereal Disease Research Laboratory; WBC—white blood cell.

CNS [1,11,23]. How effectively *T. pallidum* is cleared by host defenses in the immunosuppressed patient, and in HIV-infected patients specifically, is unknown. The lack of significant CNS penetrance by drug may allow the HIV-infected patient with syphilis to be at greater long-term risk of neurosyphilis. A third reason that many experts are in favor of performing lumbar punctures on all HIV coinfected patients is that treatment of symptomatic neurosyphilis often does not lead to a return to normal function. As such, it is reasonable to be more aggressive in making the diagnosis while infection is asymptomatic, thus improving treatment outcomes with respect to long-term morbidity [24].

Laboratory Diagnosis of Neurosyphilis

The diagnosis of all stages of syphilis, including neurosyphilis, remains subject to certain limitations, in part, because *T. pallidum* cannot be cultured in vitro. Therefore, clinicians must rely on serologic tests to confirm the diagnosis of most cases of syphilis. Unfortunately, there is no single laboratory test that can be used alone to diagnose neurosyphilis. The lack of such a definitive single test that is highly sensitive and specific often makes the diagnosis of neurosyphilis a challenge for clinicians. The "gold standard" for diagnosis of neurosyphilis is the rabbit infectivity test (RIT), in which patient CSF is inoculated into laboratory rabbits and *T. pallidum* is identified in subsequent evaluations of the animal. Given that performance of the RIT is impractical, the diagnosis of neurosyphilis is usually made by interpreting the clinical presentation, serologic test results, and spinal fluid examination in tandem. The CDC has recommended specific diagnostic criteria for neurosyphilis, which are outlined in Table 2 [20••]. These include the presence of compatible clinical signs and serologic confirmation of infection with a reactive nontreponemal serologic test (RPR or VDRL) and a reactive specific treponemal test such as the fluorescent treponemal antibody absorption (FTA-Abs), *T. pallidum* particle agglutination (FTA-Abs DS, TP-PA), or enzyme immunaoassay (EIA), along with one of the following abnormalities on spinal fluid examination: increased CSF protein greater than 40 mg per dL; increased CSF leukocyte count greater than 5 mononuclear cells per mm^3; or a reactive VDRL-CSF slide test. Alternatively, the diagnosis of neurosyphilis can be made when *T. pallidum* is identified in CSF or CNS tissue by microscopy or molecular methods [20••,23]. When a patient has clinical signs, a positive serologic test result, and an increased CSF protein or increased CSF WBC count but does not have a positive VDRL-CSF, the patient is classified as having "probable" neurosyphilis [25,26••].

In the United States, the VDRL slide test (VDRL-CSF) is the most common test used to confirm neurosyphilis. A reactive result is diagnostic for neurosyphilis, as the test is highly specific (99.8%). However, its sensitivity is only approximately 50%, and thus a nonreactive result does not exclude the diagnosis of neurosyphilis [25,26••]. False-positive results may occur if visibly bloody CSF specimens are submitted to the laboratory for testing (such as after a traumatic lumbar puncture) because of serum antibody crossing the blood-brain barrier and contaminating the CSF specimen [14,27]. It is the lack of sensitivity that makes the VDRL-CSF test less than ideal in the diagnosis of neurosyphilis.

Some specialists recommend performing the more sensitive (100%), but less specific (94%), FTA-Abs test on CSF specimens to confirm neurosyphilis and emphasize that a nonreactive result excludes the diagnosis [20••,26••]. In contrast, others do not recommend the test because it may be reactive in patients with treated secondary or latent syphilis and no signs of neurosyphilis [26••]. The FTA-Abs-CSF test is more technically complex compared with the VDRL-CSF slide test, and it is performed in few clinical or reference laboratories in the United States. Given its complexity and infrequent use, the test was not included in a recent College of American Pathologists (CAP) laboratory proficiency testing survey for syphilis serology [28]. Additionally, at the present time, the FTA-Abs test is neither US Food and Drug Administration (FDA) approved nor manufacturer recommended for testing of CSF specimens (Personal communication, Zeus Diagnostics; Personal communication, Scimedx Corporation). Despite the test's limitations and the relative paucity of laboratories where the test is reliable performed, the FTA-Abs-CSF test may occasionally be useful, particularly in excluding the diagnosis of neurosyphilis [12•,29]; its use should be considered only in specific clinical situations.

There are other laboratory tests that have been used in the diagnosis of neurosyphilis over the years, although they are less common than the standard CSF tests and not as widely used. Because the VDRL-CSF is insensitive and because the increase of CSF protein and WBC counts can be nonspecific, clinicians have tried to develop other methods to establish the diagnosis. In the United States, some specialists recommend using the intrathecally produced *T. pallidum* antibody (ITPA) index or *T. pallidum* hemagglutination assay (TPHA) index. These tests use the serologic tests and index them to concentrations of other CSF proteins as an indication of intrathecal *T. pallidum* antibody synthesis [26••] and are thought to compensate for

possible serum antibody contamination of CSF when testing for neurosyphilis [14]. However, the ITPA index and its modifications have been shown to have poor specificity (42.6% to 53.7%) and variable sensitivity (63.3% to 90%) [30]. This is not surprising because intrathecal synthesis of *T. pallidum*–specific antibody is found in only 75% of patients with neurosyphilis and in 25% of clinically asymptomatic patients; therefore, it is not very useful for diagnosis [27].

The TPHA index calculations can be based on results of the treponemal MHA-TP test (Fujirebio Diagnostics Inc., Fairfield, NJ) [13,14]. However, the MHA-TP test is neither FDA approved nor recommended by the manufacturer for use on CSF specimens, and it has recently been replaced by the TP-PA test (Fujirebio Diagnostics Inc.). The TP-PA test uses gelatin particles, instead of red cells, sensitized with *T. pallidum* antigens; the gelatin particles provide improved reagent stability. The TP-PA test, like its MHA-TP predecessor, is neither FDA approved nor recommended by the manufacturer for use on CSF specimens (Personal communication, Fujirebio Diagnostics Inc.). The TPHA index is occasionally positive in patients in whom CSF is otherwise normal. Given this finding, some specialists have recommended the test as a modality that may help in excluding the diagnosis of neurosyphilis [23,26••]. Because of all of these concerns, the TPHA index is rarely used at present in the United States.

However, in other countries, such as the United Kingdom, the TPHA index is based on the TPHA passive hemagglutination test (Oxoid, Hampshire, UK). According to the manufacturer, this test may be performed on CSF specimens, but it is not FDA approved for use in clinical diagnostic testing in the United States (Personal communication, Oxoid). According to a recent study in Europe, a TPHA index of more than 70 and a TPHA titer of more than 1:320 have a specificity of 100% and a sensitivity of 98.3% for the diagnosis of neurosyphilis [30], a significantly higher sensitivity compared with the VDRL-CSF test. Additional studies are needed to confirm the sensitivity and specificity of the TPHA index using the TPHA passive hemagglutination test. Should this method truly have such improved sensitivity compared with the VDRL, its application in the diagnosis of neurosyphilis may become more common in the near future.

Currently, in the United States, treponemal EIA tests have been FDA approved for screening and/or confirmatory testing of syphilis using serum and/or plasma specimens [25]. EIA tests use recombinant antigens or *T. pallidum* sonicates to detect specific antibodies. The two most commonly used EIA tests according to a recent CAP laboratory proficiency testing syphilis serology survey, Trep-Chek (Phoenix Bio-Tech Corporation, Mississauga, Canada) and the Captia Syphilis-G test (Trinity Biotech, Dublin, Ireland) [28], are neither FDA approved nor recommended by the manufacturer for testing CSF specimens (Personal communication, Phoenix Bio-Tech Corporation; Personal communication, Wampole Laboratories). Further studies of EIA tests using CSF specimens are needed.

Molecular tests based on the polymerase chain reaction (PCR) for the diagnosis of neurosyphilis using CSF specimens have been in use in research studies since 1991, and various test modifications using unique gene targets have subsequently been developed [26••,31]. Currently, all PCR tests are considered experimental [25]. One study demonstrated that all patients who had been previously infected with *T. pallidum* were positive by PCR, regardless of previous treatment status [32]. Additionally, because it is currently not possible to differentiate between small numbers of viable treponemes and dead organisms by PCR, and because controversy exists concerning the elimination of *T. pallidum* in the CNS after therapy, further studies must be performed to determine the clinical utility of PCR testing on CSF specimens for the diagnosis of neurosyphilis [26••]. A new research PCR test has been developed at the CDC in Atlanta, GA, which targets the DNA polymerase I gene of *T. pallidum*, and it has been tested on CSF specimens [33]. However, at this time, no PCR test for clinical use and diagnosis of neurosyphilis is offered by the CDC (Personal communication, CDC).

Thus, even in 2005, the diagnostic armamentarium for neurosyphilis is less than ideal. The perfect test would be 100% specific and sensitive, minimally invasive, and would have a rapid turnaround time in the laboratory. Additionally, such a test should be a definitive marker that could also be used in the follow-up of patients after therapy has been completed. Such an ideal test has not yet been discovered.

While the currently available diagnostic tests for neurosyphilis remain less than ideal and clinicians may become frustrated with their lack of sensitivity or specificity, the ultimate goals regarding diagnosis must not be forgotten. In the pre-antibiotic era and now, the goal of clinicians is to establish or exclude the diagnosis of neurosyphilis because of the therapeutic implications. Therapy can potentially and dramatically impact on the patient's long-term morbidity. It is important to recognize that the most important goal in the diagnosis of neurosyphilis is to identify disease so therapy can be provided before irreversible CNS damage occurs, or to halt further progression of disease.

Interpretation of Diagnostic Tests in Neurosyphilis

The diagnostic criteria for neurosyphilis listed in Table 2 were developed by expert consensus and not through prospective scientific research. There is no criterion standard to apply to the interpretation of CSF results. Most agree that the CDC criteria are reasonable for symptomatic patients without HIV coinfection. However, in the "asymptomatic" patient and in the presence of HIV infection, the interpretation of CSF may become more challenging and difficult. HIV itself will cause an increase of the CSF

protein, particularly in later stages of infection [34]; HIV may also cause an increase in WBCs in the CSF, usually early in HIV infection [35]. Thus, if the earlier criteria are applied, one might expect to overdiagnose HIV-infected patients with neurosyphilis. Some experts would counter that there is no downside to the overdiagnosis and that additional intravenous antimicrobial therapy may be beneficial because it will definitively achieve treponemicidal concentrations in the CNS, thus eradicating any *T. pallidum* that may be present [14]. However, unnecessary intravenous antimicrobial therapy should be avoided when possible, because there are potential adverse outcomes associated with a 10- to 14-day treatment course, including excess health care costs, need for an intravenous access, risk of acquisition of bloodstream infection secondary to the catheter, and inconvenience.

Some experts advocate different criteria for diagnosis of neurosyphilis in those coinfected with HIV infection, taking into account the possibility that HIV infection may increase CSF protein and/or lead to CSF pleocytosis. For example, in a recent review of syphilis, the authors stated they diagnose neurosyphilis in their asymptomatic HIV-infected patients when the patient has a positive CSF FTA-Abs result plus an increased CSF WBC count of more than 5 cells per μL [12•]. In another published study of patients with non-neurologic syphilis who had one of the CDC criteria for indication for lumbar puncture, the authors defined neurosyphilis as a positive VDRL-CSF result or a CSF pleocytosis of more than 20 cells per μL [21•]. The authors used these criteria to diagnose patients who were HIV infected and those not infected with HIV. In this study, none of the patients had signs or symptoms of neurosyphilis.

Should clinicians apply these authors' diagnostic criteria in their own practice? What conclusions, if any, may be drawn from this information? One thing is clear—there is no consensus among experts about how best to diagnose neurosyphilis, particularly in those HIV coinfected and in the subset of patients who do not have signs and symptoms of CNS disease, the so-called asymptomatic neurosyphilis patients. Consultation with an expert is recommended when interpreting CSF findings in all patients in whom the diagnosis of neurosyphilis is being considered.

As noted in the earlier text, the CDC criteria do not provide recommendations on patients without clinical signs and symptoms of neurosyphilis. One of the many uncertainties about neurosyphilis is how and when to consider the diagnosis of asymptomatic neurosyphilis. Patients with asymptomatic neurosyphilis have no signs or symptoms of disease, but an abnormal CSF is present. Whether the CSF abnormalities will eventually become progressive and lead to symptomatic illness, and in whom this is most likely to occur, are unknown. In the study by Marra *et al*. [21•], the same diagnostic criteria were applied to all patients (HIV and non-HIV) with non-neurologic syphilis who underwent a lumbar puncture; a positive VDRL-CSF or a CSF pleocytosis of greater than 20 cells per mL was consistent with neurosyphilis. In the update article, the authors used a positive CSF FTA-Abs result, with a positive CSF pleocytosis (as defined as > 5 cells/μL) or an increased CSF protein more than 45 mg per dL, to define neurosyphilis in asymptomatic non–HIV-infected individuals [12•]. Again, there is no consensus on how best to interpret the CSF findings in patients, regardless of HIV infection, who do not have the usual signs and symptoms of CNS syphilis.

Treatment of Neurosyphilis

The mainstay of therapy for all forms of syphilis infection, including CNS manifestations, is penicillin G. *T. pallidum* is a slowly dividing organism, and as such, any efficacious antimicrobial must have a prolonged exposure time to eradicate all slowly dividing organisms [23]. BPG, the first-line therapy for primary, secondary, and latent syphilis, does have the desired pharmacokinetic properties to treat neurosyphilis. When specifically treating neurosyphilis, the antimicrobial must also achieve treponemicidal concentrations in the CSF. BPG does not achieve adequate CSF concentrations for eradication of *T. pallidum* [22]. In contrast, intravenously administered penicillin does [20••]. Intravenous aqueous crystalline penicillin G, administered as a total daily dose of 18 to 24 MU (in divided doses every 4 hours) for 10 to 14 days, is the preferred regimen recommended by the CDC in its most recent 2002 treatment guidelines [20••] but may also be administered as a 24-MU continuous infusion. This particular drug, dosing schedule, and duration of therapy have never been studied in prospective randomized controlled trials; long-standing clinical experience, case series, small clinical trials, and expert consensus are the basis for these specific recommendations.

An acceptable alternative in patients with neurosyphilis who refuse to undergo intravenous therapy is procaine penicillin 2.4 MU administered once daily through intramuscular injection, with oral probenecid 500 mg four times daily, for a 10- to 14-day treatment period [20••]. However, some patients cannot tolerate the discomfort associated with the daily intramuscular injections and discontinue this regimen. Patients with allergy to sulfonamides also cannot receive probenecid and may not receive this treatment option.

The recommended duration of therapy for neurosyphilis is 10 to 14 days; this duration is not based on research data. Studies in the 1950s determined that a minimum of 8 days of antibiotic at treponemicidal levels in the CSF were required [14]. Some experts think that after completion of the 10- to 14-day regimen for neurosyphilis, the patient should then receive additional BPG intramuscularly, based on the rationale that the total duration of treatment for neurosyphilis should not be less than what would be administered for latent disease (which is a 21-day course of therapy administered as weekly injections over 3 consecutive weeks) to ensure adequate therapy for slowly dividing treponemes that may persist [23]. Therefore, some specialists recommend BPG, 2.4 MU intramuscularly once

per week for up to 3 weeks after completion of these neurosyphilis treatment regimens to provide a comparable total treatment duration.

In the penicillin-allergic patient, desensitization to penicillin is recommended [20••]. Nonpenicillin-based therapies for neurosyphilis have never been evaluated in large or small prospective treatment trials and are not routinely recommended as alternative treatment regimens. For example, doxycycline (in a 400-mg daily total dose) has been shown to achieve reliable CSF concentrations when administered orally and was effective in the treatment of patients with neurosyphilis in a small study [36,37]. However, the paucity of any additional data on doxycycline makes its use in the treatment of neurosyphilis unsupported and not recommended.

Of all of the nonpenicillin therapies, perhaps ceftriaxone is the most attractive alternative therapy. Ceftriaxone has been shown to kill *T. pallidum* in animal models [38]. It has excellent CSF penetration, achieving concentrations within the CSF well above the minimum inhibitory concentration for *T. pallidum* [39]. It also has a longer half-life than most penicillins and cephalosporins. Ceftriaxone has been studied as treatment for various stages of syphilis, including small case series in patients with neurosyphilis [40–43]. In the most recent CDC guidelines, it is suggested that ceftriaxone may be used as an alternative treatment for patients with neurosyphilis [20••]. The recommended dosage is 2 g intravenously or intramuscularly for 10 to 14 days [20••]. There may be a potential for crossreactivity between ceftriaxone and penicillin. If concern exists regarding the safety of ceftriaxone in a patient with penicillin allergy and neurosyphilis, the patient should have skin testing to confirm penicillin allergy, and if necessary, be desensitized [44•].

The use of adjunctive steroids in the treatment of hearing loss due to syphilis has been advocated but never proven effective in more than 50% of patients [14,17]. Their use is not recommended in the most recent CDC treatment guidelines [20••].

Follow-up of Patients After Completing Treatment of Neurosyphilis

In patients with neurosyphilis who are treated, the CSF leukocyte count usually normalizes first, followed by the protein concentration and then the VDRL slide test result [26••]. If CSF pleocytosis was present at the time of diagnosis of neurosyphilis, it is recommended that repeat CSF examinations be performed every 6 months until the cell count is normal [12•,20••]. Follow-up CSF examinations can also be used to monitor changes in the VDRL-CSF or CSF protein after therapy; however, changes in these two parameters occur much slower and may not be as clinically relevant [26••]. If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered [20••]. In one recent study of patients who were treated for neurosyphilis and followed with repeated lumbar punctures, those who were also HIV infected were less likely to normalize their VDRL-CSF over time [45]; this trend appeared to be more prominent when CD4 counts were less than 200 cells per μL. The CSF WBC counts did normalize similarly in HIV-infected and -uninfected patients in this study. Whether the VDRL-CSF findings indicate treatment failure or just a slower return to baseline is currently not known.

Conclusions

The changing epidemiology of syphilis in the United States and the increasing rates of infection in MSM and HIV-infected individuals must be recognized by clinicians. Screening for syphilis should be implemented in all at-risk individuals. In the MSM population, screening should be performed yearly. Neurosyphilis may present in early or late syphilis infection, and the issue of asymptomatic neurosyphilis continues to be somewhat enigmatic. Limitations in the currently available diagnostic tests for neurosyphilis, and the use of somewhat imprecise diagnostic criteria, highlight the urgent need for better diagnostic technology. Penicillin continues to be the drug of first choice for treatment of neurosyphilis; however, therapy with ceftriaxone appears promising and has recently been recommended as a potential alternative to penicillin.

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