Neurosyphilis: A Historical Perspective and Review

Khalil G. Ghanem

Johns Hopkins University School of Medicine, Baltimore, MD, USA

Keywords

Neurosyphilis; Penicillin; Review; Syphilis; *Treponema pallidum*.

Correspondence

Khalil G. Ghanem, M.D., Ph.D., Johns Hopkins University School of Medicine, JHUBMC, ID Division, 4940 Eastern Ave, B3N, Suite 352, Baltimore, MD 21224, USA.
Tel.: (410) 550-0515;
Fax: (410) 550-1169;
E-mail: kghanem@jhmi.edu

doi: 10.1111/j.1755-5949.2010.00183.x

SUMMARY

Treponema pallidum subspecies *pallidum*, the causative agent of syphilis, disseminates to the central nervous system within days after exposure. Clinical manifestations can occur during any stage of the infection, and include asymptomatic neurosyphilis, acute meningal syphilis, meningovascular syphilis, parietic neurosyphilis, and tabetic neurosyphilis. The majority of cases are reported in HIV-infected patients but the epidemiology of modern neurosyphilis is not well defined because of the paucity of population-based data. Decreasing reports of late neurosyphilis have been countered with increasing reports of early neurologic involvement. This review summarizes the clinical manifestations, diagnosis, and therapy of neurosyphilis, focusing on areas of continued controversy, and highlighting several important questions that remain unanswered. Since 2000, the rates of syphilis continue to increase. Given the effectiveness of penicillin therapy, these trends suggest a failure of prevention. Regrettably, rather than become an infection of historical significance, syphilis in the era of HIV continues to challenge researchers and clinicians.

Introduction

Treponema pallidum subspecies *pallidum*, the causative agent of syphilis, disseminates systemically hours to days after inoculation [1,2]. Early invasion (not necessarily “involvement”) of the central nervous system (CNS) is thought to occur in many (if not most) patients infected with syphilis. Thus, it is not surprising that neurological manifestations of syphilis can and do occur during any stage of the infection.

In the United States, the rates of syphilis have been increasing since 2000 [3]. The majority of new cases first occurred in men, but in the past 2 years, an increasing number of cases have been reported in women and infants born to infected mothers. There have been no recent population-based studies of neurosyphilis. After the introduction of penicillin in the 1940s, the number of cases of neurosyphilis decreased precipitously. In a retrospective Danish study of all cases of neurosyphilis diagnosed between 1971 and 1979, only 50 cases were reported to the centralized health system, and of those, the majority likely represented persons who were reinfected following appropriate penicillin therapy but were never

retreated [4]. In the HIV era, many reports of neurosyphilis cases were published, particularly of early neurosyphilis [5–7], but the lack of large-scale population studies has hindered our ability to accurately assess modern epidemiological trends.

The goal for this review is to summarize the data on neurosyphilis: its pathophysiology, epidemiology, clinical manifestations, and approach to diagnosis and therapy. As with syphilis in general, data on neurosyphilis are based on case series and individual reports, which were reviewed and are summarized herein. Most of the large series were reported in the prepenicillin era, when serological tests and therapy differed hindering the extrapolation of some of the results. For example, the Wasserman test, a complement fixation test, predated the two nontreponemal specific (or “lipoidal”) flocculation tests that we now commonly use, the Venereal Diseases Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) [8–10]. Although all of these tests detect similar nonspecific antibodies that may be elevated in syphilis, the performance measures of these tests may vary. Similarly, epidemiological studies with long-term follow-up conducted in the prepenicillin era included patients who were treated

with regimens of varying effectiveness. Their outcomes may not necessarily apply to those persons treated with penicillin. Finally, the advent of HIV in the 1980s, and its inexorable link with and impact on syphilis has further complicated matters [11–13]. The reader must be aware of these limitations. This review does not focus on neurosyphilis in the HIV-infected patient; a separate article dealing with this topic would be forthcoming.

Neuroinvasion

Treponemes are detected within minutes in lymph nodes and within hours in the cerebrospinal fluid (CSF) of rabbits following exposure to *T. pallidum* [14,15]. Investigators hypothesized that the CNS was involved early in the course of syphilis [16]. A study of 34 persons without neurological symptoms or CSF abnormalities and who had untreated early syphilis was conducted in 1924 to determine the extent of CSF invasion by treponemes [1]. Using the rabbit infectivity test (an “insensitive” gold standard which demonstrates the presence of viable *T. pallidum* strains by assessing for the development of orchitis following inoculation of infected fluid into the testes of rabbits), 15% of persons were shown to harbor *T. pallidum* in their CSF. This is probably a significant underestimate given the lack of sensitivity of the rabbit infectivity test. In a similar study of 58 patients (40 with primary and secondary, 3 with early latent, and 15 with late latent syphilis) conducted in the antibiotic era, 30% of persons with early syphilis had *T. pallidum* detected in their CSF but none of those with latent syphilis did [2]. The latter study included both symptomatic and asymptomatic patients some of whom had detectable CSF abnormalities (positive CSF VDRL, pleocytosis, and/or elevated protein concentration) and were HIV infected. There was no difference in the detection of *T. pallidum* in the CSF between HIV-infected and uninfected persons. Fifty percent of patients with neurological symptoms had detectable *T. pallidum* versus 26% of asymptomatic persons. No single CSF abnormality (or combination) was associated with isolation of *T. pallidum* (the small sample size may have limited the power to detect meaningful associations). Polymerase chain reaction (PCR) has also been used in research settings to detect *T. pallidum* DNA from CSF [17,18]. In one study, 25% (4 of 16) of patients with primary and secondary syphilis, and 29% (2 of 7) with early latent syphilis had *T. pallidum* DNA detected in their CSF [17]. Unlike the previous study that found no evidence of *T. pallidum* in the CSF of patients with late asymptomatic infection, 2 of 3 patients with late latent infection had detectable CSF *T. pallidum* DNA by PCR. These data suggest that central nervous invasion may occur

early in the course of *T. pallidum* infection, but Moore’s hypothesis that neuroinvasion occurs almost universally among persons infected with *T. pallidum* has yet to be verified objectively [19]. These data also demonstrate that *T. pallidum* may be detected in the absence of CSF abnormalities. The long-term prognosis of patients with detectable *T. pallidum* and a normal CSF is not known. It is assumed that, in most patients, *T. pallidum* is cleared from the CNS; failure of the immune system to clear the organism is thought to result in neurologic complications (Figure 1).

Asymptomatic Neurosyphilis

Asymptomatic neurosyphilis (ANS) is defined by the presence of CSF abnormalities consistent with neurosyphilis (see the section “Diagnosis” below) in persons with serological evidence of syphilis and no neurological signs or symptoms [20]. In contrast to symptomatic neurosyphilis, rates of ANS decrease as the duration of syphilis infection increases; however, ANS does occur in both early and latent stages of syphilis. In a series of 5293 patients with all stages of syphilis from the preantibiotic era (some of whom had received treatment with a variety of agents used at the time, including bismuth, heavy metals, and arsphenamine), 13.5% had ANS [21]. There were significant differences based on the stage of syphilis. In a study limited to 352 patients with primary and secondary syphilis [20], 20% of persons had at least one abnormality on CSF examination. Among 1216 persons with latent syphilis and no evidence of symptomatic neurological disease, 13.5% were found to have evidence of ANS [22]. Those with latent syphilis and ANS were more likely to have syphilitic involvement of the skin. The peak incidence of ANS occurred 12–18 months after infection and declined thereafter [22].

In the preantibiotic era, lack of response to therapy (as measured by the failure of the Wasserman test to revert back to negative) increased the probability of underlying ANS among patients with early syphilis [23–25, pp. 540–541]. That association was less pronounced among persons with late syphilis who did not respond to therapy (these data are the basis for the current recommendation to perform a CSF examination in persons with syphilis whose RPR titers do not decline 4-fold in response to therapy, see later) [25, pp. 540–541, 26].

The clinical importance of diagnosing ANS was clear in the preantibiotic era. Persons with any stage of syphilis and evidence of ANS had a significantly higher probability of developing late neurological complications than those whose CSF examination was normal [26]. Moreover, the extent of abnormalities in the CSF

Figure 1 Neurological involvement in syphilis; the estimates reflect the probability of progressing to each stage, and the brackets on the right provide the average time to progression. Note, the figure assumes no therapeutic intervention (i.e. natural progression).

correlated with the probability of developing late neurological complications. In a study of 123 persons with long-term follow-up, Moore et al. divided patients into three groups based on the extent of CSF abnormalities: the first group consisted of persons with few CSF abnormalities (white blood cell [WBC] count between 5 and 10 cells/mL and/or a slightly elevated protein); the second group consisted of persons with more pronounced abnormalities (WBC count between 10 and 50 cells/mL, higher protein concentrations, or a weakly positive CSF Wasserman test), and the third group consisted of persons with significant abnormalities (WBC count >50 cells/mL, elevated protein concentration, and a positive CSF Wasserman test) [25, p. 353]. The probability of developing late neurosyphilis in these three groups was 14.3%, 23%, and 72%, respectively, compared to <10% among persons with a normal CSF examination. These data suggested that the presence and extent of CSF abnormalities, irrespective of syphilis stage, significantly impact long-term prognosis.

The clinical significance of detecting ANS in the penicillin era is unknown. There have been no studies comparing long-term outcomes following therapy with one of the recommended antibiotic regimens in patients with and without asymptomatic CSF abnormalities. The issue lost relevance after the introduction of penicillin in the 1940s and the subsequent decline in cases of late neurosyphilis [4]. However, this issue has resurfaced with the

increased reporting of neurological complications in HIV-infected persons [7,27].

Early Symptomatic Neurosyphilis (Acute Syphilitic Meningitis or “Neurorecurrence”)

Early symptomatic neurosyphilis involves diffuse inflammation of the meninges resulting in signs and symptoms of meningitis: headache, photophobia, nausea, vomiting, cranial nerve palsies, and occasionally seizures [28]. It is diagnosed within 12 months after infection but it was infrequently diagnosed in the pre-HIV era. Merritt et al. identified only 80 cases from three general hospitals over a 15-year period starting in 1920, and only 37 cases (1.4%) among 2263 patients seen at Boston City Hospital [29, p. 28]. The majority of cases of acute syphilitic meningitis reportedly occurred after the inadequate treatment of early syphilis [30,31]. Indeed, Moore suggested that its incidence increased 10-fold in that setting [25, p. 419]. Ehrlich coined the term “neurorecurrence” after observing that the majority of cases of acute syphilitic meningitis occurred following failed therapy for early syphilis. The hypothesis was that the immune system held early *T. pallidum* infection in check, but after exposure to drugs, systemic disease was suppressed thereby diminishing the immune response and

inhibiting its ability to control *T. pallidum* in the CNS [12,25, p. 419]. In the pre-HIV penicillin era, acute syphilitic meningitis was extremely rare suggesting that the combination of a robust immune system and an excellent drug (even a drug such as benzathine penicillin G [BPG] that did not penetrate the CSF to achieve treponemidal levels) was enough to control early CNS infection. This changed, however, in the HIV era when cases of acute syphilitic meningitis in penicillin-treated and untreated persons with early syphilis were reported [6,32]. Indeed, in some reports, early symptomatic neurosyphilis was the primary neurologic manifestation of *T. pallidum* infection in HIV-infected persons [7].

Meningovascular Syphilis

Meningovascular syphilis consists of endarteritis of vessels anywhere in the CNS resulting in thrombosis and infarction. This manifestation tends to occur 5–12 years after initial infection with *T. pallidum* [33,34]. In the pre-antibiotic era, 3.2% [29, p. 89] to 15% [25, p. 366] of persons infected with syphilis developed meningovascular manifestations depending on whether pathologic criteria or clinical criteria were used to make the diagnosis. The specificity of a clinical diagnosis in a younger patient with no cerebrovascular risk factors is higher than in an older patient with underlying risk factors such as hypertension and diabetes. Early symptoms, when they occurred, included headache, vertigo, and insomnia. In over 75% of persons, the onset was sudden (often referred to as “syphilitic apoplexy”). The symptoms depended on the site of thrombosis—the majority involving the middle cerebral artery or its branches; in an analysis of 42 cases, Merritt reported that 26 involved the middle cerebral artery, and 5 involved the basilar artery [29, pp. 95–98]. Thus, the most likely manifestations included contralateral hemiplegia, hemi anesthesia, homonymous hemianopsia, and aphasia. If the pathology involved the spinal cord vessels, syphilitic meningomyelitis (most common, presenting as spastic weakness of the legs, sphincter disturbances, sensory loss, and muscle atrophy) and spinal vascular syphilis, which resulted in infarction of the anterior, or less commonly, the posterior spinal artery were the most frequently reported manifestations [35].

In the antibiotic era, mirroring the decline in neurosyphilis cases in general, the rates of meningovascular syphilis have declined. Two reports of all neurosyphilis cases in Denmark from 1971 to 1997 suggest that meningovascular syphilis makes up about 10% of modern neurosyphilis cases [4,36].

Parenchymatous Syphilis

Parenchymatous syphilis manifests as two processes: paretic neurosyphilis (a.k.a. “general paralysis of the insane,” general paresis, or “dementia paralytica”) and tabetic neurosyphilis (a.k.a. “tabes dorsalis” or “progressive locomotor ataxy”).

General Paresis

Merritt paraphrased Osler’s dictum on syphilis to “know paretic neurosyphilis in all its aspects and you know all of psychiatry.” The clinical manifestations of general paresis are protean [29, p. 175]. Symptoms are divided into early symptoms and late symptoms; the onset of the disease may be insidious or sudden. Early symptoms include irritability, forgetfulness, personality changes, headaches, and changes in sleep habits. Late symptoms include emotional lability, impaired memory and judgment, disorientation, confusion, delusions, and occasionally seizures. Psychiatric manifestations range from depression, to delirium (hallucinations), mania, and psychosis [37, p. 903]. Common neurological signs include pupillary abnormalities (Argyll–Robertson pupils occur in late paresis but are more often observed in tabes Dorsalis [38]), dysarthria, and tremors of facial, lingual, and hand muscles. Rarely, optic atrophy and ocular muscle palsies were also described. Pathologically, there is atrophy of the frontal and temporal lobe with sparing of the motor, sensory, and occipital cortex. This leads to dilatation of the lateral ventricles. The “Lissauer” form of the disease, which occurs much less frequently, may also affect the cerebellum and basal ganglia. There is evidence of chronic meningitis, most intense over the atrophic areas. Up to 100% of autopsy specimens were found to harbor spirochetes by tissue staining [29, p. 176]. The spirochetes were mainly noted in the gray matter and also within endothelial cells and microglial cells. No spirochetes were found in the white matter. Whether the pathological changes are due to a direct parenchymal effect or the impact of the spirochetes on the cerebral vasculature, or both, is unclear. Merritt estimated that 5% of patients infected with syphilis in the preantibiotic era ultimately developed paresis. The average time from infection to onset of paretic neurosyphilis is between 15 and 20 years [33,34]. Most untreated patients with general paresis died within 5 years after the onset of symptoms.

In the antibiotic era, although rates of neurosyphilis have declined, cases of paretic neurosyphilis misdiagnosed as primary neuropsychiatric diseases still occur. In one of the largest modern case series of tabetic neurosyphilis [39] reported in 1969, 91 patients from 6 hospitals in the United Kingdom were assessed. One-third

presented with depression and psychotic features, 20% presented with dementia, 20% presented with psychosis and concomitant tabes, and 11% presented with manic features. Twenty percent of patients died; 20% required persistent hospitalization for the psychiatric symptoms, and the remainder required occasional hospitalizations for acute exacerbations of symptoms.

Tabes Dorsalis

Romberg was the first to describe the classic manifestations of tabes dorsalis— the ataxic gait, lightning pains, paresthesias, bladder dysfunction, and failing vision (optic atrophy) [40]. Signs include pupillary abnormalities (Argyll Robertson pupils being the most common [38]), diminished reflexes, impaired vibratory sense and proprioception, ocular palsies, and Charcot's joints. Pathologically, there is degeneration of the posterior roots and column of the spinal cord. Tabes dorsalis affected 3–9% of persons infected with syphilis [29, p. 245]. The average time from infection to onset of tabetic neurosyphilis is between 20 and 25 years [33,34].

Gumma of the CNS

Gummas of the CNS occurred rarely even in the pre-antibiotic era when up to 10% of adults in urban areas were infected with syphilis [29, p. 62]. The manifestations were typical of a space-occupying lesion. Gummas occurred anywhere in the brain or spinal cord. Manifestations depended on the particular location. Cases have been reported among HIV-infected persons [41].

Clinical Manifestations of Neurosyphilis in the Antibiotic Era

The availability of antibiotics has led to a precipitous decline in the incidence of neurosyphilis [4,36,42]. Some hypothesized that the widespread use of antibiotics for a variety of infections unrelated to syphilis would result in incomplete or partial treatment of patients with undiagnosed underlying syphilis and potentially lead to a change in the clinical manifestations of neurosyphilis. Indeed, several case series purported to describe these atypical or “formes frustes” [42–46]. Mainly, they reported more subtle and monosymptomatic presentations. Such presentations, however, were well described in the pre-antibiotic era [37, p. 905] and reports of these atypical manifestations in the antibiotic era have been very limited.

In one of the largest modern case series evaluating all patients diagnosed with neurosyphilis in Denmark

between 1980 and 1997, 92 cases were described [36]. Data were available on 77 patients; 33% were HIV-infected. Twenty-seven percent were categorized as ANS, 10% meningovascular, 50% parenchymatous, and the rest could not be categorized. A similar Danish study conducted between 1970 and 1979 reported similar findings except for a lower prevalence of parenchymatous neurosyphilis [4]. There was no clear evidence of atypical presentations or “formes frustes.”

In the HIV era, several reports suggested an increase in the incidence in early neurosyphilis compared to late neurosyphilis [5–7]. Whether this is due to antibiotic exposure to treat unrelated infections, or due to the immunosuppression associated with HIV infection is unclear. An increase in ocular manifestations of syphilis has also been reported [47–49]. In addition, neurosyphilis presentations that mimic herpes simplex encephalitis have been described [50,51]. Patients were young, and often presented with seizures and parenchymal abnormalities on neuroimaging (reviewed by Marra [52]).

Diagnosis

Diagnostic Criteria

There is/are no gold standard test(s) to diagnose neurosyphilis. The Centers for Disease Control and Prevention (CDC) has established surveillance definitions that are mainly used epidemiologically [53]. The two categories are “confirmed” neurosyphilis and “presumptive” neurosyphilis. The former is defined as (1) any stage of syphilis and (2) a reactive CSF VDRL. Presumptive neurosyphilis is defined as (1) any stage of syphilis, (2) a nonreactive CSF VDRL, (3) CSF pleocytosis or elevated protein, and (4) clinical signs or symptoms consistent with syphilis without an alternate diagnosis to account for these.

Serologic Testing

Two types of serologic tests are necessary to make a diagnosis of syphilis [54]. In the United States, the nonspecific lipoidal tests (the RPR and VDRL) are usually chosen as the screening test, and treponemal-specific tests are performed as confirmatory tests in response to a positive lipoidal test. The nontreponemal serological test titers are followed after therapy to document response. Response is defined as a 4-fold decline in titers following therapy. For early syphilis, a 4-fold decline in titers is expected 6–12 months after therapy. For late stage disease, a decline is expected 12–24 months after therapy [55]. Serologic response, however, does not necessarily imply a microbiologic cure. The relationship between serology

and microbiology is unclear. Lack of serologic response may be due to either treatment failure or reinfection. The distinction between these two events is very difficult to make given the challenges of obtaining reliable information from persons on their sexual behaviors. Treponemal-specific tests become positive in the primary stage of infection and, in general, remain so for life.

The sensitivity of lipoidal tests in diagnosing syphilis depends primarily on the stage of infection. Sensitivity is only 70% in primary syphilis, but 100% in secondary syphilis and early latency [54]. Over time, the natural history of the lipoidal test titer is to decline, even in the absence of antibiotic therapy. Thus, over time, the sensitivity of the lipoidal test to detect untreated late syphilis diminishes. Hence, when diagnosing early neurosyphilis, the serum lipoidal test is almost always positive. When diagnosing late neurosyphilis, the serum lipoidal tests may be negative in up to 30% of persons. If clinical suspicion for late neurosyphilis is high, a treponemal test should be obtained even when the lipoidal test is negative.

In the preantibiotic era, there was a clear association between the serum lipoidal positivity, and the risk of developing late neurological complications [56]. Persons with early syphilis who did not manifest complete lipoidal test reversions at the end of therapy (i.e., those who had a persistently positive titer—also referred to as a “sero-fast” titer) had a 3-fold increased risk of late neurological complications compared to those whose lipoidal titers reverted to negative after therapy. The clinical significance of persistently positive lipoidal titers in the antibiotic era is unknown. The current view is that a 4-fold decline in lipoidal titers is sufficient to define cure, even if the lipoidal titers remain positive thereafter [55].

A topic of persistent controversy is the value of routine syphilis serological screening in the workup of dementia and psychiatric conditions [57–60]. Given the declining incidence of neurosyphilis, the likelihood of detecting untreated late neurosyphilis as a reversible cause in these settings is extremely low. In the 2001 Report of the Quality Standards Subcommittee of the American Academy of Neurology for the diagnosis of dementia, routine screening for syphilis was not recommended [61]. This was based on the observation that rates of syphilis were declining. Given that rates of syphilis have been steadily increasing since 2000, this topic continues to elicit some controversy.

The CSF Examination

In the preantibiotic era, Merritt summarized the approach to the CSF examination: “The status of the CSF should be known in all cases of syphilis whether or not symptoms or signs of involvement of the nervous system are

manifest and regardless of the stage of the disease” [29, p. 359]. The reason was simple: in an era with imperfect drugs, the CSF examination predicted long-term outcomes. Persons with early syphilis and a normal CSF examination at 6 months were unlikely to progress to symptomatic neurosyphilis unless their serum Wassermann titers increased [62]. In patients with a negative CSF examination 4 years after initial infection, the likelihood of developing long-term neurological complications was less than 1%.

After the introduction of penicillin, and despite the use of therapeutic regimens that did not achieve treponemidal levels in the CSF [63], the rates of neurosyphilis plummeted [4]. As a result, clinicians abandoned routine CSF examination despite the occasional echo of dissent. There has never been any controversy about the need for a CSF examination in patients with serological evidence of syphilis and neurological signs or symptoms suggestive of neurosyphilis. The controversy has focused on the need for CSF examination among asymptomatic patients. The CDC’s position in the pre-HIV era was summarized in Harold Jaffe’s 1982 article [64]: “For neurologically normal patients with early syphilis, CSF examination is unnecessary ... For neurologically normal patients with syphilis of more than one year’s duration, the need for CSF examination is an unsettled issue.” Even though asymptomatic CSF abnormalities may be present early in the course of the infection, Jaffe argued, most resolved in a short period of time and the penicillin-based treatment schedules recommended at that time appeared to be effective [65]. Indeed, progression to late neurosyphilis had not been reported after appropriate penicillin therapy (note that at the time that Jaffe’s paper was published, it was known that BPG did not consistently penetrate the CSF). The argument clearly did not take into account Moore’s data showing that early CSF abnormalities predicted development of late neurological complications [26].

The uncertainty surrounding CSF examination in patients with syphilis of more than 1-year duration was, at the crux of it, uncertainty about the efficacy of BPG in treating ANS. Several factors favored routine CSF examination in latent syphilis: in addition to various studies that demonstrated conclusively the lack of adequate CSF penicillin concentrations to achieve treponemal killing when using BPG [63,66,67], a study by Smith et al. showed that 20% of patients with early syphilis who were treated with 2.4 million units (MU) of BPG had persistent CSF abnormalities consistent with ANS 18 months after therapy [68]. This finding stood in sharp contradistinction to the findings of several studies that reported normal CSF parameter 1–2 years after the treatment of early syphilis using higher doses of short-acting

penicillin formulations [69–71]. The major factor that put into doubt the need for CSF examination was the observation that between 1959 and 1980, there had been no reported cases (in the literature or to the CDC) of late neurosyphilis that developed among patients with ANS treated with the recommended penicillin regimens (including BPG) [64]. One case reported in 1980, in retrospect, was most likely an HIV-infected person [72]. In 1985, an analysis of the risks and benefits of performing a CSF examination in asymptomatic patients with syphilis of more than 1-year duration showed that the CSF examination would not lead to an increase in cure rates but may be associated with a higher rate of morbidity [73]. Prior to the advent of HIV, and despite these uncertainties, CSF examination was almost never performed among neurologically asymptomatic patients. Had it not been for the appearance of HIV in the early 1980s, and the multiple reports of treatment failures associated with the CDC-recommended penicillin regimens [32,74,75], CSF examination would probably never figure in the modern algorithm to manage syphilis.

The 2006 CDC Treatment Guidelines recommend that a CSF examination be performed in all patients (1) with serological evidence of syphilis and neurological symptoms and (2) when serological titers among asymptomatic patients do not respond appropriately to recommended therapeutic regimens [55]. In other words, CSF examination should be performed in all asymptomatic patients with early syphilis whose RPR titers fail to demonstrate a 4-fold or greater decline 6–12 months after therapy, in patients with late latent syphilis whose RPR titers fail to demonstrate a similar decline 12–24 months after therapy, or in any stage patient whose titers increase 4-fold after appropriate therapy. The latter recommendation is based in preantibiotic era data suggesting a higher risk of ANS among patients with early syphilis whose lipoidal test titers did not serorevert or increased after therapy [25]. Whether these data are applicable to patients treated with standard doses of penicillin is unknown given the lack of modern data on this topic.

To summarize, the debate surrounding CSF examination in patients with syphilis is the result of uncertainty about the clinical relevance of ANS in the penicillin era. The debate had begun to subside, but the HIV epidemic reignited it. In the preantibiotic era, a robust immune system, in the presence of inadequate therapies, was often incapable of preventing neurological complications. In the antibiotic era, a robust immune system combined with penicillin, even at doses that are not treponemical in the CSF, lead to excellent outcomes. The destruction of the immune system by HIV demonstrates that penicillin alone is not enough to prevent neurological

complications of syphilis. Thus, prevention of neurological complications requires good drugs and a robust immune system. When one or both factors are missing, more careful evaluation (e.g., CSF examination) is probably warranted.

CSF Pleocytosis

The CSF pleocytosis in syphilis is lymphocyte-predominant. Polymorphonuclear lymphocytes may predominate, especially in acute syphilitic meningitis. A cutoff of greater than or equal to 5 cells/mL has been the standard. That cutoff has less specificity among HIV-infected persons due to nonspecific abnormalities associated with HIV-infection itself [76]. Limited data suggest that a cutoff of 10 cells/mL for HIV-infected persons on antiretroviral therapy, and 20 cells/mL for those not on antiretroviral therapy may improve the specificity for diagnosing neurosyphilis [77].

In early syphilis, a slight pleocytosis may be the only sign of CNS involvement. There is a marked pleocytosis (up to 2000 cells/mL) in patients with acute meningeal syphilis. In tabetic and parietic patients, the average number of cells is 25–75 cells/mL. In up to 10% of patients with tabes, the CSF cell count may be normal. This is often referred to as the “burned out” stage of tabes.

CSF Protein

The CSF protein mainly consists of albumin and globulins in a 4:1 ratio. With inflammation, both fractions increase, with the globulins increasing more than albumin. Prevalence of abnormalities in the CSF protein concentration varies depending on the clinical form of neurosyphilis. In syphilitic meningitis, 12% of patients have a CSF protein ≤ 45 mg/dL while 34% with meningo-vascular syphilis, 25% with general paresis, and 47% with tabes do [78]. The protein concentration cutoff used as a diagnostic marker for neurosyphilis varies depending on the laboratory.

CSF Lipoidal and Treponemal-Specific Tests

Treponemal nonspecific (lipoidal) and specific serological tests have been used on the CSF to establish a diagnosis of neurosyphilis. The nonspecific Wasserman test, which predated the VDRL and RPR tests, was routinely used to help establish a diagnosis of neurosyphilis. The data on the CSF Wassermann are more comprehensive than the very limited data we have on the CSF VDRL and CSF RPR. Among patients with early ANS, a positive CSF Wassermann test increased the likelihood of developing future neurologic complications [23,25, pp. 351–353]. Noteworthy, is that even with a

negative Wassermann test, in the presence of CSF pleocytosis and/or protein abnormalities, there was still an increased risk of progression to symptomatic neurosyphilis, albeit to a lesser degree. Also of note, in some cases, positive CSF Wassermann tests predated a positive serum Wassermann test. False positive CSF Wassermann tests were described in patients with leprosy, trypanosomiasis, and cerebral malaria [79]. The Wassermann test was negative in many patients with early syphilis who were neurologically asymptomatic, but whose CSF exhibited either pleocytosis or elevated protein concentrations suggestive of neuroinvasion [19]. Among patients with early syphilitic meningitis, the Wassermann test was positive in 86% of patients [28]. The CSF Wassermann reaction was nearly always positive in patients with general paresis (the positivity of the CSF Wassermann was one of the hallmarks of the “paretic formula” which also included a mild pleocytosis of up to 75 cells/mL and an increased protein concentration) [29, p. 375]. In patients with tabes, up to 28% of patients had a negative CSF Wassermann test, particularly in the later stages of tabes (often referred to as “burned out tabes”) [29, p. 375].

The first modern nonspecific test for syphilis, the VDRL, continues to be the standard test used today. A positive CSF VDRL in a patient with syphilis of any stage defines a “confirmed” case of neurosyphilis [53]. However, the sensitivity of the VDRL has been an issue of debate. Just like the Wassermann test, the VDRL is not positive in all cases of neurosyphilis. Exactly what percentage of patients with neurosyphilis have a negative CSF VDRL is a matter of debate. That controversy peaked in 1972 after the publication of one of the largest modern case series of neurosyphilis [45]. Hooshmand et al. presented data on 241 patients diagnosed with neurosyphilis over a 5-year period at the Medical College of Virginia. In 43% of the cases, the CSF VDRL was nonreactive. Whether many of these patients had neurosyphilis at all was a matter of debate. When comparing the CSF Wassermann data and the VDRL data, there was clearly a discrepancy. Although 10–28% of patients with neurosyphilis in the preantibiotic era had a negative CSF Wassermann [25, pp. 351–353, 29, pp. 374–379], the Hooshmand data suggested that almost twice as many patients had a negative CSF VDRL. The reason for the discrepancy was never elucidated; some argued that the case selection was unreliable [80] while others suggested that this was the result of exposure to antibiotics that have antitreponemal activity [46,81]. In summary, a positive VDRL establishes a diagnosis of neurosyphilis, but a negative VDRL does not exclude it.

The use of the CSF RPR instead of the VDRL is not currently recommended. One study showed similar performance measures between the CSF VDRL and CSF RPR.

[10] An earlier study, however, had found that the RPR was less specific. The studies used different methods to prepare the antigens. At this time, the CSF VDRL is still considered the lipoidal test of choice.

After the serum fluorescent treponemal antibody (FTA) test was introduced and found to be more sensitive than the serum lipoidal tests, it was used on CSF samples. Early studies demonstrated that the CSF-FTA tests appeared to be more sensitive than the CSF lipoidal tests. Indeed, in the Hooshmand paper described above, 100% of the 241 patients have a positive CSF-FTA test. The main issue that arose was its specificity when testing CSF. Jaffe et al. found that 30% of patients with serological evidence of syphilis and normal CSF parameters were found to have a positive CSF-FTA [82]. Positivity correlated with higher serum titers. Among 177 nonsyphilitic patients, one was found to have a positive CSF-FTA test. Similar findings were reported for the second generation FTA-Abs test [83,84]. At this time, the CDC does not recommend using treponemal-specific tests on the CSF, as a positive result may not reflect neurosyphilis. A negative CSF-FTA Abs, however, may be reasonable to rule out neurosyphilis.

Several studies have evaluated the performance measures of detecting intrathecal production of *T. pallidum*-specific IgG in the diagnosis of neurosyphilis, but data have been inconsistent [85–88].

In summary, there is no gold standard test to diagnose neurosyphilis. The diagnosis must be based on a combination of laboratory tests and clinical findings. Although the CSF VDRL is helpful to confirm neurosyphilis, its absence may not rule it out.

Brain Imaging

There are no pathognomonic radiographic findings that suggest a diagnosis of neurosyphilis. In a series of 14 HIV-uninfected patients with neurosyphilis who underwent computed tomography and/or magnetic resonance imaging, the most common radiographic findings included frontal and temporo-parietal atrophy with nonspecific white matter lesions in 4 patients with tabes dorsalis. In 6 patients with meningovascular syphilis, imaging demonstrated nonspecific changes consistent with infarction (mainly middle cerebral artery distribution). One patient with acute syphilitic meningitis had evidence of meningeal enhancement. Two patients with ANS had nonspecific white matter changes, and another had normal imaging. In another study of 20 HIV-uninfected patients with psychiatric manifestations of paretic neurosyphilis, 13 were noted to have MRI abnormalities [89]. The most common findings were generalized cerebral atrophy and foci of increased signal intensity

on T-2-weighted images. There was a significant association between the presence of frontal lesions and overall degree of psychiatric morbidity. There was also evidence of increasing cognitive impairment in patients with more advanced atrophy.

Treatment

Since its introduction in the 1940s, penicillin remains the mainstay of therapy to treat neurosyphilis. The ideal dose of penicillin is not known as no randomized comparative trials were done, but the dose increased from 2.4 MU in the 1940s [90] up to 336 MU today [55]. What became clear early on was that higher doses of penicillin for a longer duration yielded the greatest impact on serological tests and CSF abnormalities [91].

Over the next 30 years, different penicillin doses and preparations were used with various estimates of success depending on the outcome measure chosen and the duration of follow-up [92]. Today, the recommended treatment regimen for neurosyphilis is 18–24 MU of intravenous aqueous penicillin G daily, either as a continuous infusion, or divided every 4 h, for 10–14 days [55]. An alternate regimen is 2.4 MU of intramuscular procaine penicillin daily plus 500 mg oral probenecid four times a day for 14 days. Limited data on the use of ceftriaxone suggest that 1–2 g intravenously or intramuscularly for 10–14 days yields acceptable results [93–97]. Some experts recommend one to three additional dose of 2.4 MU of intramuscular BPG at the end of any 14-day antibiotic course to ensure appropriate duration of therapy for underlying latent syphilis.

Of historical interest, 3 weekly doses of 2.4 MU of BPG intramuscularly was an alternate recommended treatment option for neurosyphilis through the 1970s. However, in the late 1970s, reports surfaced that these doses did not achieve consistent treponemicidal levels in the CSF. Despite decades of use for neurosyphilis, and good clinical responses [98], the recommendation to use 3 doses of 2.4 MU of BPG was ultimately abandoned in favor of different penicillin preparations and higher overall doses. Whether treponemicidal doses in the CSF are needed to control neurosyphilis among patients with a robust immune system is a question that lingers to this day.

The goal of therapy is to inhibit the progression of the infection and to try and reverse symptoms. Response to therapy depends on the stage of infection. In patients with early meningeal neurosyphilis, quick resolution of symptoms is the rule [78] (except in HIV-infected patients who may have persistent signs and symptoms for greater than 1 year after therapy [7]). For late disease, especially

the parenchymatous forms, resolution of symptoms may not occur [99,100].

Data on the treatment of psychiatric symptoms associated with parietic neurosyphilis are very limited. In 1 case series, there appeared to be benefit with the judicious use of some of the newer psychotropic medications [101]. The authors recommended the use of the lowest effective doses of neuroleptic agents, and periodic attempts to reduce their doses to minimize side effects.

Follow-up

The CDC recommends follow-up CSF examinations every 6 months until CSF abnormalities have resolved [55]. If by the end of 2 years, CSF abnormalities have not resolved, retreatment for neurosyphilis is recommended. In a recent study, Marra et al. found that a 4-fold decline in serologic RPR titers correlated with resolution of CSF parameters in persons with neurosyphilis who were not HIV-infected [102].

Conclusions

Many fundamental questions about the diagnosis and management of neurosyphilis persist. Our inability to culture *T. pallidum* has hindered progress in the field. We still rely upon indirect measures to gauge disease activity. Regrettably, far from becoming an infection of historical significance, the rates of syphilis continue to increase. HIV has now added another layer of complexity. By destroying the immune system, it may have unmasked some of the limitations of penicillin that a robust immune system had kept veiled.

Conflict of Interest

The authors have no conflict of interest.

References

1. Chesney AM, Kemp JE. Incidence of *Spirochaeta pallida* in cerebrospinal fluid during early stage of syphilis. *J Am Med Assoc* 1924;**83**:1725–1728.
2. Lukehart SA, Hook EW, 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by *Treponema pallidum*: Implications for diagnosis and treatment. *Ann Intern Med* 1988;**109**:855–862.
3. Centers for Disease Control and Prevention. *Sexually transmitted disease surveillance 2008*. Atlanta, GA: Department of Health and Human Services, 2009.
4. Perdrup A, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark: A clinical and serological

- study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. *Acta Derm Venereol Suppl (Stockh)* 1981;**96**:1–14.
5. Flood JM, Weinstock HS, Guroy ME, Bayne L, Simon RP, Bolan G. Neurosyphilis during the AIDS epidemic, San Francisco, 1985–1992. *J Infect Dis* 1998;**177**: 931–940.
 6. Centers for Disease Control and Prevention (CDC). Symptomatic early neurosyphilis among HIV-positive men who have sex with men – four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep* 2007;**56**:625–628.
 7. Ghanem KG, Moore RD, Rompalo AM, Erbeling EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS* 2008;**22**:1145–1151.
 8. Moore JE, Eagle H. The quantitative serologic test for syphilis, its variability, usefulness in routine diagnosis, and possible significance, a study of 1665 cases. *Ann Intern Med* 1941;**14**:1802–1814.
 9. Portinoy J, Garson W, Smith CA. Rapid plasma reagin test for syphilis. *Public Health Rep* 1957;**72**:761–766.
 10. Castro R, Prieto ES, Pereira Fd LM. Nontreponemal tests in the diagnosis of neurosyphilis: An evaluation of the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) tests. *J Clin Lab Anal* 2008;**22**:257–261.
 11. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med* 1990;**113**:872–881.
 12. Musher DM. Syphilis, neurosyphilis, penicillin, and AIDS. *J Infect Dis* 1991;**163**:1201–1206.
 13. Zetola NM, Klausner JD. Syphilis and HIV infection: An update. *Clin Infect Dis* 2007;**44**:1222–1228.
 14. Raiziss GW, Severac M. Rapidity with which *Spirochaeta pallida* invade the bloodstream. *Arch Derm Syphilol* 1937;**35**:1101–1109.
 15. Collart P, Franceschini P, Durel P. Experimental rabbit syphilis. *Br J Vener Dis* 1971;**47**:389–400.
 16. Widal F. Cytologie du liquide cephalo-rachidien des syphilitiques. *Soc Med Des Hop* 1902;**3**:531–539.
 17. Chung KY, Lee MG, Lee JB. Detection of *Treponema pallidum* by polymerase chain reaction in the cerebrospinal fluid of syphilis patients. *Yonsei Med J* 1994;**35**:190–197.
 18. Centurion-Lara A, Castro C, Shaffer JM, Van Voorhis WC, Marra CM, Lukehart SA. Detection of *Treponema pallidum* by a sensitive reverse transcriptase PCR. *J Clin Microbiol* 1997;**35**:1348–1352.
 19. Moore JE. The genesis of neurosyphilis. *Arch Derm Syphilol* 1921;**4**:55–61.
 20. Keidel A, Moore JE. Studies in asymptomatic neurosyphilis I: A tentative classification of early asymptomatic neurosyphilis. *Arch Neurol Psychiatry* 1921;**6**:286–291.
 21. O'Leary PA, Cole HN, Moore JE, et al. Cooperative clinical studies in the treatment of syphilis: Asymptomatic neurosyphilis. *Arch Derm Syphilol* 1937;**35**:387–401.
 22. Moore JE. Asymptomatic neurosyphilis V: A comparison of early and late asymptomatic neurosyphilis. *Arch Derm Syphilol* 1928;**18**:99–108.
 23. Goodman MJ, Moore JE. Persistent abnormalities (Wassermann-fastness) of the spinal fluid in treated neurosyphilis: Their prognostic import. *Arch Intern Med* 1935;**55**:826–833.
 24. Moore JE, Padgett P. The problem of seroresistant syphilis. *JAMA* 1938;**110**:96–100.
 25. Moore JE. *The modern treatment of syphilis*, 2nd ed. Baltimore: Charles C. Thomas, 1943.
 26. Moore JE, Hopkins HH. Asymptomatic neurosyphilis VI: The prognosis of early and late asymptomatic neurosyphilis. *J Am Med Assoc* 1930;**95**:1637–1641.
 27. Marra CM. Deja vu all over again: When to perform a lumbar puncture in HIV-infected patients with syphilis. *Sex Transm Dis* 2007;**34**:145–146.
 28. Merritt HH. The early clinical and laboratory manifestations of syphilis of the central nervous system. *N Engl J Med* 1940;**223**:446–450.
 29. Merritt HH, Adams RD, Solomon HC. *Neurosyphilis*. New York: Oxford University Press, 1946.
 30. Zimmermann EL. Neurorecurrences following treatment with arsphenamin. *Arch Derm Syphilol* 1922;**5**:723–733.
 31. Moore JE. The relation of neurorecurrences to late syphilis: A clinical study of eighty-one cases. *Arch Neurol Psychiatry* 1929;**21**:117–136.
 32. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis: Its occurrence after clinical and serologic cure of secondary syphilis with penicillin-G. *Arch Neurol* 1986;**43**:137–138.
 33. Clark EG, Danbolt N. The Oslo study of the natural history of untreated syphilis; an epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material: A review and appraisal. *J Chronic Dis* 1955;**2**:311–344.
 34. Rockwell DH, Yobs AR, Moore MB Jr. The Tuskegee study of untreated syphilis: The 30th year of observation. *Arch Intern Med* 1964;**114**:792–798.
 35. Adams RD, Merritt HH. Meningeal and vascular syphilis of the spinal cord. *Medicine* 1944;**23**:181–214.
 36. Danielsen AG, Weismann K, Jorgensen BB, Heidenheim M, Fugleholm AM. Incidence, clinical presentation and treatment of neurosyphilis in Denmark 1980–1997. *Acta Derm Venereol* 2004;**84**:459–462.
 37. Stokes JH. *Modern clinical syphilology*. Philadelphia, PA: W.B. Saunders Company, 1926.
 38. Merritt HH, Moore M. The Argyll Robertson pupil: An anatomic-physiologic explanation of the phenomenon,

- with a survey of its occurrence in neurosyphilis. *Arch Neurol Psychiatry* 1933;**30**:357–373.
39. Dewhurst K. The neurosyphilitic psychoses today: A survey of 91 cases. *Br J Psychiatry* 1969;**115**:31–38.
 40. Romberg EH. Pupillary disturbances in tabes. *Zeitschrift Fur Die Gesamte Neurologie Und Psychiatrie* 1939;**165**:369–372.
 41. Weinert LS, Scheffel RS, Zoratto G, Samios V, Jeffmann MW, Dora JM, Goldani LZ. Cerebral syphilitic gumma in HIV-infected patients: Case report and review. *Int J STD AIDS* 2008;**19**:62–64.
 42. Kofman O. The changing pattern of neurosyphilis. *Can Med Assoc J* 1956;**74**:807–812.
 43. Joffe R, Black MM, Floyd M. Changing clinical picture of neurosyphilis: Report of seven unusual cases. *Br Med J* 1968;**1**:211–212.
 44. Joyce-Clarke N, Molteno AC. Modified neurosyphilis in the Cape Peninsula. *S Afr Med J* 1978;**53**:10–14.
 45. Hooshman H, Escobar MR, Kopf SW. Neurosyphilis: Study of 241 patients. *J Am Med Assoc* 1972;**219**:726–729.
 46. Hotson JR. Modern neurosyphilis: A partially treated chronic meningitis. *West J Med* 1981;**135**:191–200.
 47. Parc CE, Chahed S, Patel SV, Salmon-Ceron D. Manifestations and treatment of ocular syphilis during an epidemic in France. *Sex Transm Dis* 2007;**34**, 553–556.
 48. Fonollosa A, Giralt J, Pelegrin L, Sánchez-Dalmau B, Segura A, García-Arumí J, Adan A. Ocular syphilis—back again: Understanding recent increases in the incidence of ocular syphilitic disease. *Ocul Immunol Inflamm* 2009;**17**:207–212.
 49. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis* 2010;**37**:41–43.
 50. Szilak I, Marty F, Helft J, Soeiro R. Neurosyphilis presenting as herpes simplex encephalitis. *Clin Infect Dis* 2001;**32**:1108–1109.
 51. Bash S, Hathout GM, Cohen S. Mesiotemporal T2-weighted hyperintensity: Neurosyphilis mimicking herpes encephalitis. *AJNR Am J Neuroradiol* 2001;**22**:314–316.
 52. Marra CM. Update on neurosyphilis. *Curr Infect Dis Rep* 2009;**11**:127–134.
 53. Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. *MMWR Recomm Rep* 1990;**39**:1–43.
 54. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev* 1995;**8**:1–21.
 55. Centers for Disease Control and Prevention; Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2006;**55**:1–94.
 56. Moore JE, Padgett P. The problem of seroresistant syphilis (so-called Wassermann fastness). *J Am Med Assoc* 1938;**110**:96–100.
 57. van de Ree MA, Stam J, Hische EA, van Ketel RJ. Routine screening for syphilis in neurology is not useful. *Ned Tijdschr Geneeskde* 1992;**136**:1356–1359.
 58. Montejó M, Ruiz-Irastorza G, Aguirrebengoa K, Onate J, Aurrekoetxea J. Neurosyphilis as a cause of dementia: Does it still exist? *J Infect* 1995;**30**:186–187.
 59. Frank C. Dementia workup: Deciding on laboratory testing for the elderly. *Can Fam Physician* 1998;**44**:1489–1495.
 60. Polsky I, Samuels SC. Neurosyphilis: Screening does sometimes reveal an infectious cause of dementia. *Geriatrics* 2001;**56**:60–62.
 61. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;**56**:1143–1153.
 62. Hopkins HH. Prognostic import of a negative spinal fluid in early and in latent syphilis. *Arch Derm Syphilol* 1931;**24**:404–408.
 63. Mohr JA, Griffiths W, Jackson R, Saadah H, Bird P, Riddle J. Neurosyphilis and penicillin levels in cerebrospinal-fluid. *JAMA* 1976;**236**:2208–2209.
 64. Jaffe HW, Kabins SA. Examination of cerebrospinal-fluid in patients with syphilis. *Rev Infect Dis* 1982;**4**:S842–S847.
 65. Hahn RD, Cutler JC, Curtis AC, et al. Penicillin treatment of asymptomatic central nervous system syphilis. 1: Probability of progression to symptomatic neurosyphilis. *Arch Derm* 1956;**74**:355–366.
 66. Dunlop EMC, Alegaily SS, Houang ET. Penicillin levels in blood and CSF achieved by treatment of syphilis. *JAMA* 1979;**241**:2538–2540.
 67. Polnikorn N, Witoonpanich R, Vorachit M, Vejajiva S, Vejajiva A. Penicillin concentrations in cerebrospinal-fluid after different treatment regimens for syphilis. *Br J Vener Dis* 1980;**56**:363–367.
 68. Smith CA, Kamp M, Olansky S, Price EV. Benzathine penicillin G in the treatment of syphilis. *Bull World Health Organ* 1956;**15**:1087–1096.
 69. Altshuler L, Karpinos BD. Efficacy of penicillin treatment of early syphilis in the Army. *Am J Syph Gonorrhea Vener Dis* 1949;**33**:126–138.
 70. Fernando WL. Cerebrospinal fluid findings after Treatment of early syphilis with penicillin. *Br J Vener Dis* 1965;**41**:168–169.
 71. Fernando WL. Cerebrospinal fluid findings after treatment of early syphilis with penicillin: A further series of 80 cases. *Br J Vener Dis* 1968;**44**:134–135.
 72. Greene BM, Miller NR, Bynum TE. Failure of penicillin-G benzathine in the treatment of neurosyphilis. *Arch Intern Med* 1980;**140**:1117–1118.
 73. Wiesel J, Rose DN, Silver AL, Sacks HS, Bernstein RH. Lumbar puncture in asymptomatic late syphilis: An analysis of the benefits and risks. *Arch Intern Med* 1985;**145**:465–468.

74. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med* 1987;**316**:1587–1589.
75. Berger JR. Neurosyphilis in human immunodeficiency virus type 1-seropositive individuals: A prospective study. *Arch Neurol* 1991;**48**:700–702.
76. 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**:219–221.
77. Marra CM, Maxwell CL, Collier AC, Robertson KR, Imrie A. Interpreting cerebrospinal fluid pleocytosis in HIV in the era of potent antiretroviral therapy. *BMC Infect Dis* 2007;**7**:37.
78. Simon RP. Neurosyphilis. *Arch Neurol* 1985;**42**:606–613.
79. Merritt HH. Neurosyphilis and its treatment. *N Engl J Med* 1939;**221**:817–819.
80. Musher DM. Neurosyphilis: Diagnosis and response to treatment. *Clin Infect Dis* 2008;**47**:900–902.
81. Burke JM, Schaberg DR. Neurosyphilis in the antibiotic era. *Neurology* 1985;**35**:1368–1371.
82. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med* 1978;**138**:252–255.
83. Hunter EF, Deacon WE, Meyer PE. An improved FTA test for syphilis, the absorption procedure (FTA-ABS). *Public Health Rep* 1964;**79**:410–412.
84. McGeeney T, Yount F, Hinthorn DR, Liu C. Utility of the FTA-ABS test of cerebrospinal-fluid in the diagnosis of neurosyphilis. *Sex Transm Dis* 1979;**6**:195–198.
85. Vartdal F, Vandvik B, Michaelsen TE, Loe K, Norrby E. Neurosyphilis: Intrathecal synthesis of oligoclonal antibodies to *Treponema pallidum*. *Ann Neurol* 1982;**11**:35–40.
86. Prange HW, Moskophidis M, Schipper HI, Muller F. Relationship between neurological features and intrathecal synthesis of IgG antibodies to *Treponema pallidum* in untreated and treated human neurosyphilis. *J Neurol* 1983;**230**:241–252.
87. Moskophidis M, Peters S. Comparison of intrathecal synthesis of *Treponema pallidum*-specific IgG antibodies and polymerase chain reaction for the diagnosis of neurosyphilis. *Zentralbl Bakteriol* 1996;**283**:295–305.
88. Ebinger M, Grauer MT, Uhr M. Intrathecal IgA synthesis in neurosyphilis. *J Neurol Sci* 2005;**228**:21–25.
89. Russouw HG, Roberts MC, Emsley RA, Truter R. Psychiatric manifestations and magnetic resonance imaging in HIV-negative neurosyphilis. *Biol Psychiatry* 1997;**41**:467–473.
90. Stokes JH, Sternberg TH, Schwartz WH, Mahoney JF, Moore JE, Wood WB. The action of penicillin in late syphilis including neurosyphilis, benign late syphilis and late congenital syphilis: Preliminary report. *J Am Med Assoc* 1944;**126**:73–80.
91. Moore JE. Penicillin in syphilis: A 1947 appraisal. *Trans Assoc Am Physicians* 1947;**60**:172–180.
92. Idsoe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis: The experience of three decades. *Bull World Health Organ* 1972;**47**:1–68.
93. Hook EW 3rd, Baker-Zander SA, Moskovitz BL, Lukehart SA, Handsfield HH. Ceftriaxone therapy for asymptomatic neurosyphilis: Case report and Western blot analysis of serum and cerebrospinal fluid IgG response to therapy. *Sex Transm Dis* 1986;**13**(Suppl 3): 185–188.
94. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human-immunodeficiency-virus. *Am J Med* 1992;**93**:481–488.
95. Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. *Clin Infect Dis* 2000;**30**: 540–544.
96. Shann S, Wilson J. Treatment of neurosyphilis with ceftriaxone. *Sex Transm Infect* 2003;**79**:415–416.
97. Smith NH, Musher DM, Huang DB, Rodriguez PS, Dowell ME, Ace W, White AC Jr. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS* 2004;**15**: 328–332.
98. Short DH, Knox JM, Glicksma J. Neurosyphilis search for adequate treatment: A review and report of a study using benzathine penicillin G. *Arch Derm* 1966;**93**: 87–89.
99. Reynolds FW, Mohr CF, Moore JE. Penicillin in the treatment of neurosyphilis. 2: Dementia paralytica. *JAMA* 1946;**131**:1255–1260.
100. Hahn RD, Webster B, Weickhardt G, et al. Penicillin treatment of general paresis (dementia-paralytica): Results of treatment in 1,086 patients the majority of whom were followed for more than 5 years. *Arch Neurol Psychiatry* 1959;**81**:557–590.
101. Sanchez FM, Zisselman MH. Treatment of psychiatric symptoms associated with neurosyphilis. *Psychosomatics* 2007;**48**:440–445.
102. Marra CM, Maxwell CL, Tantalos LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis* 2008;**47**:893–899.