Neurosyphilis

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Semin Neurol 2019;39:448–455.

Abstract

Neurosyphilis is caused by the bacterium *Treponema pallidum* subspecies *pallidum* (*T. pallidum*). The organism gains entry into the central nervous system (CNS) early (primary syphilis or chancre phase) in the course of infection. While most patients are able to mount an immune response that effectively clears CNS invasion without long-term complications, a minority go on to develop asymptomatic or symptomatic neurosyphilis. Neurosyphilis has been divided into early and late stages. The early stages include asymptomatic meningitis, symptomatic meningitis, gumma, and meningovascular syphilis, while the late stages include dementia paralytica and tabes dorsalis. Ocular and otologic syphilis can occur at any time but often accompany the acute meningitis of early neurosyphilis. The diagnosis of symptomatic neurosyphilis requires meeting clinical, serologic, and cerebrospinal fluid (CSF) criteria, while the diagnosis of asymptomatic neurosyphilis relies on serologic and CSF criteria alone. In the last several decades, a persistent rise in syphilitic meningitis and other forms of early neurosyphilis have been seen in the human immunodeficiency virus-positive population, principally in men who have sex with men. This article reviews the clinical presentation, diagnosis, and treatment of neurosyphilis, and it addresses the controversy regarding the role of lumbar puncture early in the course of infection.

Keywords
- neurosyphilis
- asymptomatic neurosyphilis
- syphilitic meningitis

Clinical case: A 31-year-old right-handed man presents to the emergency room with 3 days of back pain, neck pain, and headaches. His temperature is 38°C. While in the emergency department he sustains a 15-minute generalized seizure. He has a remote history of intravenous (IV) methamphetamine use. Magnetic resonance imaging (MRI) shows fluid-attenuated inversion recovery (FLAIR) hyperintensities, restricted diffusion, and patchy enhancement within the medial left temporal, occipital, and parietal lobes, and the right parietal lobe (►**Fig. 1**). Cerebrospinal fluid (CSF) shows 291 white blood cells (WBCs)/µL (8% polymorphonuclear neutrophils [PMN], 79% lymphocytes, 13% macrophages), 0 red blood cells (RBCs)/µL, glucose 78 mg/dL (plasma glucose 110 mg/dL), and protein 240 mg/dL.

Pathogenesis

Historically, our understanding of neurosyphilis pathogenesis had been curtailed by the inability to culture *Treponema pallidum* in an artificial medium; however, this situation may be changing.[1] Syphilis can be acquired by person-to-person transmission, where organisms gain entry into the new host via skin microabrasions or through mucous membranes. It can also be transmitted by blood transfusion, solid organ transplant, or vertically. In a model system, treponemes cross vascular barriers by binding to endothelial cells and subsequently making their way through tight junctions in a process known as interjunctional penetration.[2]

Treponema pallidum rapidly disseminates systemically after initial infection and can affect any organ including the central nervous system (CNS).[3] In the rabbit model, *T. pallidum* is cleared from peripheral sites by opsonization, followed by ingestion and killing by activated macrophages. This is mediated by pathogen-specific immunoglobulin G and is independent of complement.[4] A similar process likely occurs in humans, and opsonic activity in peripheral blood is reduced in human immunodeficiency virus (HIV)-infected

Issue Theme Neuroinfectious Disease, Part 2; Guest Editor, Anna M. Cervantes-Arslanian, MD

DOI https://doi.org/10.1055/s-0039-1688942.
ISSN 0271-8235.

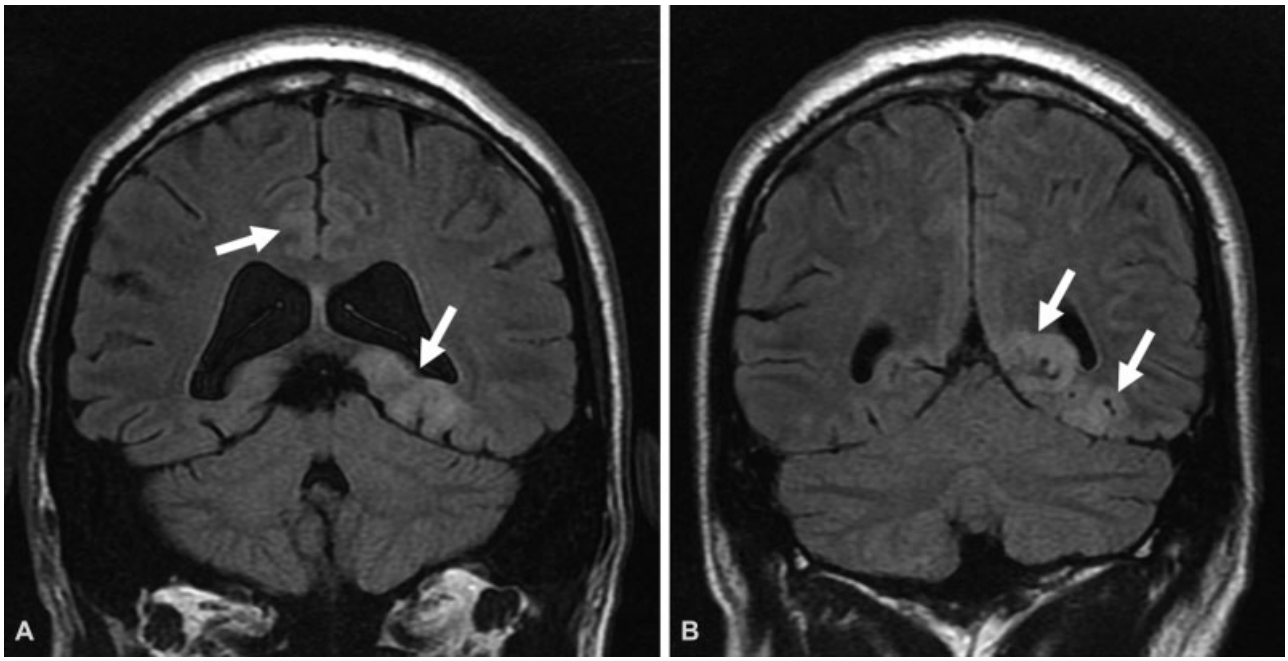

Fig. 1 (**A**) Coronal FLAIR sequence showing hyperintense signal in the left medial temporal lobe and the right medial parietal cortex (*arrows*). (**B**) Coronal FLAIR sequence showing hyperintense signal in the left medial parietal-occipital lobes (*arrows*). FLAIR, fluid-attenuated inversion recovery.

individuals with syphilis compared with HIV-uninfected individuals with syphilis.[5] A Th1-predominant immune response consisting of $CD4^+$ cells and interferon-γ (IFN-γ) has been described in cutaneous lesions of primary and secondary syphilis, further supporting the hypothesis that IFN-γ activated macrophages are primary effectors in treponeme clearance.[6] *Treponema pallidum* possesses several mechanisms that enable it to evade the host immune response, including a relatively antigen-poor surface membrane, and emergence during the course of infection of antigenically variant surface proteins.[7,8]

Detection of *T. pallidum* in the CSF of neurologically asymptomatic patients with early syphilis was shown in the pre-antibiotic era by rabbit inoculation, and in the modern era by rabbit inoculation and polymerase chain reaction (PCR), and occurs in at least 30% of individuals.[9–13] The frequency of neuroinvasion is not affected by HIV status.[3,9] Dissemination of *T. pallidum* to the CNS may spontaneously resolve. This may occur without an inflammatory response or following transient meningitis. Persistent inflammation is referred to as asymptomatic neurosyphilis.[12,13] Patients with asymptomatic neurosyphilis are at risk for symptomatic neurosyphilis. The mechanism of clearance from the CSF likely parallels that in the periphery. Specifically, in a nonhuman primate model, CSF clearance was accompanied by an influx of $CD4^+$ T lymphocytes and local production of IFN-γ.[14]

An increased risk of neurosyphilis, particularly the early forms, is seen in HIV-infected individuals,[15,16] likely resulting from a defect in immune-mediated clearance of *T. pallidum* from the CSF or CNS. Risk factors include lower peripheral blood $CD4^+$ T cell counts,[11,17] detectable plasma HIV RNA, high serum rapid plasma reagin titer (RPR),[11] and lack of antiretroviral (ARV) use.[17–19] Benzathine penicillin G for uncomplicated syphilis does not achieve treponemacidal penicillin levels in CSF, and *T. pallidum* has been isolated from CSF after as many as three weekly injections.[20] Neurological relapse is defined as development of symptomatic or asymptomatic neurosyphilis following appropriate treatment for early syphilis. Neurorelapse occurred in six out of nine HIV-infected individuals who had received adequate penicillin therapy for syphilis in one series,[21] and may occur after treatment with benzathine penicillin G or doxycycline.[9,22–26] In addition to host factors that increase neurosyphilis risk, bacterial factors may play a role. Enhanced molecular typing showed that, compared with other types, type 14df strains were more likely to cause laboratory-defined neurosyphilis.[27]

Pathology

The histologic hallmark of syphilis, regardless of anatomic site or disease state, is perivascular infiltrates containing lymphocytes, histiocytes, and plasma cells with varying degrees of endothelial cell swelling and proliferation.[28] CNS gummas are composed of a dense perivascular infiltrate of lymphocytes, plasma cells, epithelioid cells, and multinucleated giant cells surrounding a caseous, necrotic core; endarteritis is another typical feature of these lesions.[29,30] Diffuse leptomeningitis characterizes asymptomatic neurosyphilis and syphilitic meningitis. The pathologic findings of meningovascular syphilis include diffuse thickening and lymphocytic infiltration of the meninges with superimposed arteritis.[31,32] In the case of paresis, perivascular lymphocytic and plasma cell infiltration in the brain parenchyma is typically observed, with neuronal loss and atrophy.[33,34] Perivascular and intracellular, phagocytosed, iron deposition constitutes a pathognomonic finding.[35] The identification of treponemes in the cerebral cortex of

patients with general paresis has been reported.[35–37] Tabes dorsalis features demyelination, axonal degeneration, and atrophy of the posterior columns in the spinal cord.[33,38,39]

Epidemiology

The rates of primary and secondary syphilis in the United States have increased steadily since 2000.[40] In 2017, the rate was 10.5% higher than in 2016. Sixty-eight percent of patients were men who have sex with men, and 46% were persons living with HIV (PLWH).[41]

In contrast to reporting of uncomplicated syphilis, reporting of neurosyphilis is inconsistent. Of the 48,045 cases of early syphilis reported to Centers for Disease Control and Prevention (CDC) between 2009 and 2015, 403 (0.8%) cases of neurosyphilis were reported: 295 (0.6%) were confirmed and 108 (0.2%) were probable. PLWHs who had primary, secondary, and early latent syphilis had a higher prevalence of neurosyphilis (1.2%) compared with those without HIV (0.7%).[42] The true burden of neurosyphilis is likely underestimated due to variability in screening for neurological signs and symptoms and in examining CSF.

Clinical

The symptoms and signs of neurosyphilis can be divided in those that occur early (weeks to months to the first few years) and late (years to decades) after initial infection. Early neurosyphilis includes asymptomatic neurosyphilis, symptomatic (acute syphilitic) meningitis, gumma, and meningovasculitis. Late neurosyphilis includes paretic neurosyphilis and tabes dorsalis. In asymptomatic neurosyphilis, patients have serological evidence of syphilis, lack neurological symptoms, and examination of CSF reveals abnormalities, including elevated WBC or protein concentrations, or reactivity of the CSF-Venereal Disease Research Laboratory test (CSF-VDRL). In symptomatic syphilitic meningitis, symptoms include those of meningeal irritation and increased intracranial pressure such as neck pain, back pain, headache, blurry vision, nausea, and vomiting.[43] In the preantibiotic era, Merritt described the CSF findings in the three forms in which syphilitic meningitis was classified at the time: hydrocephalic, vertical, and basilar; as a composite, the range of WBC pleocytosis was 50 to 2,000 cells/mL and the protein range was 50 to 250 mg/dL. All but three of 26 patients had a positive CSF Wassermann reaction, the predecessor of the CSF-VDRL.[44]

In patients with meningovascular syphilis, signs of ischemic stroke follow a syndrome of subacute meningitis.[45] Any vascular territory serving brain or spinal cord can be affected.[46–51] Although the distribution of the middle cerebral artery is the territory most commonly affected, there are reports of posterior circulation strokes including basilar and vertebral artery occlusion.[52,53] Bilateral involvement is not uncommon, as would be expected in a CNS vasculitis. Merritt reported on the CSF findings of two patients in the prepenicillin era; one had 80 WBC/mL and the other 700 WBC/mL, the first patient had a CSF protein level of 120 mg/dL.[43] In a small French series, all five patients demonstrated a CSF profile of lymphocytic pleocytosis and normoglycorrhachia, and four had a reactive CSF-VDRL.[54] Meningovascular syphilis should be suspected in a young, sexually active individual presenting with stroke, particularly if they lack traditional cerebrovascular risk factors.

In ocular syphilis, any portion of the eye can be involved[55]; however, posterior uveitis and panuveitis are the most commonly seen syndromes. These occur most commonly in secondary syphilis but can be seen in any stage of infection.[56,57] In one case series, 12/31 (38.7%) patients with ocular syphilis who underwent lumbar puncture had a reactive CSF-VDRL.[56] The prevalence of ocular syphilis is likely higher in HIV-positive patients, particularly those with low $CD4^+$ T cell counts and detectable viral loads.[57] A cluster of ocular syphilis cases between December 2014 and March 2015 prompted the CDC to issue a clinical advisory.[58,59] A subsequent review of ocular syphilis in eight U.S. jurisdictions (California, excluding Los Angeles and San Francisco, Florida, Indiana, Maryland, New York City, North Carolina, Texas, and Washington) identified 388 individuals with suspected ocular syphilis in 2014 and 2015.[60] One half of the patients had early syphilis with a median RPR titer 128 (range: 1–16,384), and less than one-quarter reported extraocular symptoms. Half were PLWHs.

Otologic syphilis can present as an acute or insidious onset of hearing loss or vestibular dysfunction that can be unilateral or bilateral, as well as permanent or fluctuating. In one case series of 37 patients, only two (5.4%) had a reactive CSF-VDRL.[61] In another case series, a reactive fluorescent treponemal antibody absorption test (FTA-ABS) in the presence of otologic symptoms carried a sensitivity of 100% versus 55% for RPR; the positive predictive value was 22% versus 2%, respectively.[62]

CNS gummas are granulomatous growths that typically extend from the meninges and can impinge on the brain parenchyma, thus mimicking brain tumors. These can cause hydrocephalus or seizures, or may be incidental findings on brain imaging.[30,63–65] The largest case series to date reported that 61.9% (13/21) of patients with CNS gummas who underwent lumbar puncture had a reactive CSF-VDRL.[63]

Dementia paralytica presents as progressive dementia manifested as impaired memory and judgement followed by progressive disorientation, confusion, and occasional seizures. This syndrome is often heralded by psychiatric symptoms, which can range from depression to hallucinations and psychosis.[66] Common neurological signs include pupillary abnormalities (Argyll Robertson pupils are more commonly observed in tabes but can occur in late paresis), dysarthria, and tremors.[67] Parkinsonism, though rare, has been reported.[66,68–70] In the preantibiotic era, Merritt estimated that 5% of patients with syphilis would go on to develop paresis.[45] The average time from infection to the onset of paretic neurosyphilis is several decades. In a study of clinical and laboratory abnormalities in 85 patients without HIV who had paresis, 60% had CSF pleocytosis, 54% had an elevated CSF protein, and 80% a reactive CSF-RPR.[71]

Symptoms of tabes dorsalis include shooting pains and abdominal crises. Signs include sensory ataxia, areflexia, neurogenic bladder, and sexual dysfunction.[45] Argyll

Robertson pupils are identified in up to 60% of patients.[72,73] The CSF profile can be completely normal or show mild pleocytosis and protein elevation.[74,75] In a preantibiotic series of 35 cases with tabes, 20 (57.1%) had a positive CSF Wassermann reaction.[74]

Clinical case continued: An HIV serological test was positive. Peripheral blood $CD4^+$ T lymphocytes were 100/μL and plasma HIV RNA was 45,910 copies/mL. CSF PCR for herpes simplex virus (HSV), varicella zoster virus, enterovirus, parechovirus, and *Mycobacterium tuberculosis* were negative, and HSV-1 and HSV-2 antibodies were not detected in the serum. The patient remained confused but alert, and seizures were controlled with lacosamide.

Diagnosis

The diagnosis of neurosyphilis depends upon a combination of clinical findings, serological tests for syphilis, and confirmatory testing of CSF.[76] Serologic tests for syphilis are divided into treponemal and nontreponemal. The treponemal tests measure IgG and IgM antibodies to *T. pallidum* or to recombinant *T. pallidum* proteins. These include the *T. pallidum* particle agglutination (TPPA), FTA-ABS, and various *T. pallidum* enzyme immunoassays (TP-EIAs) or chemiluminescence immunoassays (CIAs).[77] Once a patient has developed treponemal antibodies, they generally remain reactive for life.[78] As such, they are a good screen for neurosyphilis because a nonreactive result means that the patient has never had syphilis and thus could not have neurosyphilis. Of note, the EIA and CIA are sensitive but not specific, and a reactive result should be confirmed with a different treponemal test that uses a different assay method.

Nontreponemal tests measure IgG and IgM antibodies to a synthetic cardiolipin-cholesterol-lecithin antigen. Results are often reported as a titer, which reflects the number of dilutions required to no longer see a flocculation reaction.[79] Nontreponemal tests include the RPR, VDRL, and toluidine red unheated serum test (TRUST), of which RPR is the most commonly used. These become reactive after the treponemal tests, with titers typically decreasing after successful treatment or following untreated infection. Success of therapy is based on the nontreponemal test response. Serological response is faster in early syphilis compared with late syphilis.

A serofast status is variably defined, but a reasonable definition is a less than fourfold (two dilution) decline in nontreponemal antibody titers at 6 to 12 months or persistent low titers after treatment that do not meet criteria for treatment failure.[80] A systematic review estimated that between 35 and 45% of individuals with syphilis remain serofast after treatment.[81] In one study of 17 patients with secondary syphilis, 13 achieved an initial fourfold decline in serum RPR but remained serofast 24 months after therapy; all 13 developed neurosyphilis as defined by: (1) new neurological or psychiatric symptoms that responded to neurosyphilis treatment, (2) new CSF pleocytosis, or (3) new elevation in CSF protein.[82] A Chinese study of 402 HIV-negative serofast individuals found that 34.6% had asymptomatic neurosyphilis based on reactive CSF-RPR or elevated CSF protein or CSF pleocytosis.[83]

Once the diagnosis of syphilis has been established by means of serological testing, CSF analysis is required to demonstrate the presence of neurosyphilis.[76] The CDC recommends that all persons with syphilis and neurological, ocular, or otologic symptoms (e.g., cognitive dysfunction, motor or sensory deficits, vision or hearing loss, cranial nerve palsies, and symptoms and signs of meningitis or stroke) undergo CSF analysis. Except in the case of tabes, it is rare to have symptomatic neurosyphilis without concomitant CSF findings. However, ocular and otosyphilis may be seen in individuals with normal CSF. One study described the proportion of individuals with CSF abnormalities in asymptomatic ($n = 40$) and symptomatic neurosyphilis ($n = 63$); data are shown in ►**Table 1**.[84] The proportion of patients with CSF abnormalities is dependent upon the criteria used to define neurosyphilis. It is important to keep in mind that individuals with HIV with high $CD4^+$ T cell counts or who are not on ARV treatment or who have detectable plasma HIV RNA may have CSF pleocytosis related to HIV alone. Thus the criteria for neurosyphilis diagnosis differ in PLWHs and those without HIV (►**Table 2**).

Nontreponemal Tests on CSF

The VDRL is the only serologic test recommended by the CDC for CSF. Although it lacks sensitivity (range: 27–82%),[79,85,86] it is very specific.[85] Alternative CSF nontreponemal tests, such as the CSF-RPR and CSF TRUST, have lower sensitivity but may have higher specificity than CSF-VDRL.[79,86–89]

Table 1 CSF abnormalities in neurosyphilis

	Asymptomatic	Symptomatic			
		Meningovascular	Paretic	Tabetic	Ocular
No. of cases	40	4	39	8	12
CSF protein, mg/dL (range)	39.6 (20–87)	50.5 (22.3–100.5)	59.5 (20–186)	33.9 (14–64)	39.5 (20–74)
CSF WBC, cells/μL (range)	4.2 (0–84)	40.7 (5.6–73.7)	5 (0–97.9)	19.8 (2–145.2)	2.75 (1–86.9)
CSF-VDRL (+) (%)	40 (100)	4 (100)	37 (94.9)	8 (100)	10 (83.3)
CSF-VDRL (−) and CSF-TPPA (+) (%)	0 (0)	0 (0)	2 (5.1)	0 (0)	2 (16.7)

Abbreviations: CSF, cerebrospinal fluid; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory; WBC, white blood cells.

Source: Taken with permission from: Wang C, Zhu L, Gao Z, et al. Increased interleukin-17 in peripheral blood and cerebrospinal fluid of neurosyphilis patients. PLoS Negl Trop Dis 2014;8(7):e3004.

Table 2 Suggested neurosyphilis diagnostic criteria

Asymptomatic neurosyphilis
Reactive serum treponemal test AND Reactive CSF-VDRL If CSF-VDRL is negative: Reactive CSF-treponemal test AND • In a patient not infected with HIV: CSF WBC $>$ 5/μL or CSF protein $>$ 45 mg/dL • In a patient who is HIV infected with peripheral blood CD4$^+$ T cells $<$ 200/μL and undetectable plasma HIV RNA and on antiretroviral therapy: CSF WBC $>$ 5/μL • In a patient who is HIV infected with peripheral blood CD4$^+$ T cells $>$ 200/μL or detectable plasma HIV RNA or not taking antiretroviral therapy: CSF WBC $>$ 20/μL
Symptomatic neurosyphilis
Reactive serum treponemal test AND Symptoms and signs of neurosyphilis AND Reactive CSF-VDRL OR CSF WBC $>$ 5/μL or CSF protein $>$ 45 mg/dL

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; RNA, ribonucleic acid; VDRL, Venereal Disease Research Laboratory; WBC, white blood cells.
Source: Taken with permission from: Marra CM. Neurosyphilis. Continuum 2015; 21(6): 1714–1728.

Treponemal Tests on CSF

The sensitivity of CSF-FTA-ABS and CSF-TPPA is superior to that of CSF-VDRL (76–95% in one study[90] and 100% in another[91]), making it useful to "rule out" neurosyphilis when negative. The use of a CSF TPPA cutoff of $\geq$1:640, in addition to CSF-VDRL, improved specificity and would have increased the number neurosyphilis diagnoses by 21.3% in one study.[90] A systematic review concluded that the sensitivity of the CSF FTA-ABS approached 100% for asymptomatic neurosyphilis, but not for the symptomatic forms.[92]

Asymptomatic Neurosyphilis and the Role of Lumbar Puncture

Debate continues over the significance of identifying asymptomatic neurosyphilis. While the CDC guidelines state that CSF examination in neurologically asymptomatic patients with syphilis is not associated with improved outcomes, it is important to realize that there are no data either way. In the preantibiotic era, routine lumbar puncture in all patients with syphilis was the norm. In the preantibiotic era, Moore and Hopkins[10] showed that neurologically asymptomatic individuals with the most abnormal CSF were at greatest risk of developing symptomatic neurosyphilis. Whether this observation remains true in the antibiotic era is unknown. Based on the data discussed above, it would be reasonable to consider lumbar puncture in high-risk PLWHs based on serum RPR titer, CD4$^+$ T cell counts, plasma HIV RNA load, and use of ARV, or in those who remain serofast after treatment, regardless of HIV status. The CDC currently recommends lumbar puncture in individuals who fail therapy.[76]

Clinical case continued: Our patient's serum TPPA test was reactive. Serum RPR was reactive at a titer of 1:32. The CSF-VDRL was reactive at a titer of 1:16. This case illustrates the proper sequence of diagnosis of neurosyphilis: the patient was first identified as having syphilis and subsequent CSF analysis fulfilled criteria for neurosyphilis. He was treated with 24 million units of IV penicillin G as a continuous infusion per day for 10 days.

Treatment

The CDC-recommended treatment regimens for neurosyphilis are aqueous crystalline penicillin G (18–24 million units per day administered intravenously as 3–4 million units every four hours or 24 million units daily as a continuous infusion for 10–14 days) or procaine penicillin G (2.4 million units intramuscularly per day) plus probenecid (500 mg orally four times a day), both for 10 to 14 days.[76] Alternative regimens include ceftriaxone 2 g intramuscularly or intravenously daily for 10 to 14 days.[93]

Ocular syphilis and otologic syphilis should be managed identically to neurosyphilis, even if the CSF examination is normal, and with the collaboration with an ophthalmologist or otologist. Topical or systemic steroids for ocular syphilis and systemic steroids for otologic syphilis are often used but no controlled trial has been conducted to date to demonstrate efficacy. Some experts advocate their use before penicillin treatment to prevent the Jarisch–Herxheimer reaction,[94] which consists of an acute febrile response occurring usually within a few hours after initiation treatment. It may occur later in CNS syphilis.[95] Several case series report varying levels of efficacy.[96–99]

Monitoring

Successful neurosyphilis treatment results in resolution of clinical and CSF abnormalities, including pleocytosis, elevated protein concentration, and CSF-VDRL reactivity. The CDC

recommends that CSF examination be repeated every 6 months after completion of therapy until abnormalities resolve. Our practice is to perform the first posttherapy lumbar puncture at 3 months after therapy to minimize loss to follow-up and to potentially identify early treatment failure (increased in CSF WBCs or fourfold increase in CSF-VDRL). CSF protein may normalize more slowly than other CSF measures.[100] Normalization of serum RPR after neurosyphilis therapy predicts normalization of CSF abnormalities in HIV-uninfected individuals and in PLWHs who are on ARV therapy.[101]

Clinical case continued: Our patient subsequently began combination ARV therapy. Three months later, peripheral blood $CD4^+$ T-cells were increased to 218/μL and plasma HIV RNA was undetectable. He had persistent memory problems but an otherwise normal neurological examination. CSF showed decreased WBC from 291 to 27 WBC/μL (97% lymphocytes, 3% macrophages), 0 RBCs/μL, glucose 76 mg/dL (plasma glucose: 95 mg/dL), and decreased protein from 240 to 76 mg/dL. CSF-VDRL and serum RPR titers were unchanged. MRI showed improvement in the previously identified abnormalities. He has not yet undergone repeat CSF examination.

Conclusions

Neurosyphilis is an important complication of syphilis that has potentially serious sequelae. Invasion of the CNS by *T. pallidum* occurs early in the course of infection, but it is generally short-lived in those with an intact immune system. In a minority of healthy patients and in particular PLWHs, the infection can persist and cause symptomatic disease, including hearing or vision loss, meningitis, stroke, dementia, or sensory and gait abnormalities. The rising trend in syphilis cases raises concern for a similar phenomenon in neurosyphilis. CSF analysis remains the cornerstone of the diagnosis, but we lack a perfect "gold standard" diagnostic test. The role of lumbar puncture in individuals with syphilis but no neurological symptoms remains a topic of debate, but risk factors for both symptomatic and asymptomatic neurosyphilis have been defined. Treatment of neurosyphilis relies on penicillin, as it has since the drug became available. Follow-up includes repeat clinical and CSF examinations to document improvement.

Conflict of Interest
Dr. Marra reports grants from NIH and personal fees from Wolters Kluwer, outside the submitted work.

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