

From our consultation files

The challenge of neurosyphilis in HIV

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Many diseases vary in their presentation when they occur in an HIV-infected patient as compared to an immunocompetent patient. The consultation line for the Delta AETC receives questions on these topics frequently with evaluation for neurosyphilis a very common topic. Syphilis is a common co-morbidity with HIV, especially in the MSM (men who have sex with men) community. MSM make up approximately 2/3 of cases of syphilis nationwide and HIV co-infection rates range from 34% in Houston to 51% in Chicago to 60% in Los Angeles and San Francisco.

The term “neurosyphilis” is frequently misunderstood to be synonymous with “tertiary syphilis” by health care personnel. Neurosyphilis is simply involvement of the central nervous system (CNS) with syphilis infection. The manifestations vary, though, and are usually divided into early neurosyphilis and late neurosyphilis. The late neurosyphilis manifestations usually manifest during the tertiary stage of syphilis and classically include dementia, general paresis, and tabes dorsalis, and are a result of extensive damage to the parynchema in the spinal cord or the cortical regions of the brain. These manifestations are rarely seen nowadays because of the extensive screening that has been done over the past two decades for syphilis.

Early neurosyphilis was unusual in the pre-HIV era but has increased dramatically in incidence over the past 25 years, especially in persons with HIV. Early infection of the CNS can result in either spontaneous resolution, asymptomatic neurosyphilis, syphilitic meningitis, or progression to late neurosyphilis. Other manifestations can include ocular and otologic problems; some examples include uveitis, optic neuritis, cranial nerve palsies (*ie* Bell’s Palsy), sensorineural hearing loss, and vertigo.

When a patient with HIV is found to have syphilis either clinically or by serologic screening, lumbar puncture must be considered. Unfortunately there is no strong guideline for determining which HIV-infected patients with syphilis need cerebral spinal fluid (CSF) analysis. The CDC takes a conservative approach and recommends lumbar punctures for all patients with ocular or neurologic symptoms, including hearing loss. The 2006 STD Treatment Guidelines also acknowledge, though, that “some specialists recommend CSF examination before treatment of HIV-infected patients with early syphilis.” Differing medical professionals use other criteria to determine a need for a lumbar puncture, such as a serum RPR titre ranging from a 1:32 up to 1:256 minimum. CD4 count cut-offs have also been used by differing clinicians, with all patients with CD4 counts less than 200 cells/ml up to 350 cells/ml receiving CSF evaluation for neurosyphilis.

Christina Marra, MD, and the clinic at the University of Washington School of Medicine in Seattle evaluated over 125 neurologically-asymptomatic HIV-uninfected subjects and 420 neurologically-asymptomatic HIV-infected person. Among the HIV-negative persons, the odds ratio of having a reactive VDRL of the CSF was 4.6 times

higher in those with serum RPR titers greater than 1:32 as compared to those with lower titers; this was *not* influenced by stage of syphilis. Among those who were HIV-infected, the odds ratio for the titer of 1:32 or higher was 7.5 that of those with titers < 1:32. Dr. Marra recommends CSF evaluation of all individuals whose RPR is greater than 1:32, regardless of HIV status and stage of syphilis; she also recommends that “ideally, all HIV-infected subjects with syphilis should undergo lumbar puncture.”

Dr. Khalil Ghanem *et al* from the Johns Hopkins University School of Medicine in Baltimore evaluated 231 cases of syphilis in an HIV-infected cohort, including 41 episodes of neurosyphilis. Patients were considered as having neurosyphilis if they had a positive CSF VDRL, CSF white blood cell count > 10/microliter, or CSF total protein > 50 mg/dl. They found that risk factors for neurosyphilis included CD4 cell counts < 350 cells/ml (OR 2.87), serum RPR > 1:128 (OR 2.83), and male sex (OR 2.46). Serologic failure of therapy was defined as a four-fold increase in serum RPR titers at least 30 days after completion of therapy, a lack of at least a four-fold decrease in serum RPR titers at least 365 days after treatment completion, or clinical manifestations compatible with syphilis.

Interpretation of CSF findings to diagnose neurosyphilis can be challenging in the HIV-infected population. A positive CSF VDRL is confirmatory for neurosyphilis but the sensitivity is low (ranging from 30-70%) and may be falsely positive if the CSF sample is visibly bloody; presumptive neurosyphilis is diagnosed by an elevated WBC or total protein in the CSF. Because HIV causes a smoldering inflammation of the brain in many patients with HIV, CSF WBC counts (usually a mononuclear predominance) and protein levels are often mildly elevated simply because of the HIV infection itself. Dr. Ghanem's study used a WBC of higher than 10 as diagnostic and a total protein level of higher than 50. This author usually uses a WBC cut-off of 20 and a total protein of 70 for diagnosis of presumptive neurosyphilis in HIV-infected patients.

In Ghanem's study, use of highly active antiretroviral therapy (HAART) before the syphilis diagnosis was associated with a 65% decrease in chance of having neurosyphilis. Since HAART will decrease the HIV viral load in the CSF of patients who are adherent to their medications, it stands to reason that WBC counts and total protein levels would be decreased for those on HAART versus those not on ART. Therefore this finding would only be relevant if there was a decrease in *confirmed* neurosyphilis incidence with positive CSF VDRL results rather than using any of the three criteria.

Syphilis is a common co-morbidity and should be screened for at least annually in all HIV-infected persons and possibly more commonly in high risk patients.

Evaluation for CNS involvement should be:

- done for all patients with neurologic abnormalities, including ocular complaints or hearing loss or vertigo regardless of the stage,
- strongly considered for all HIV-infected patients with serum RPR > 1:32 regardless of the stage,
- strongly considered for all HIV-infected patients with CD4 counts < 350 regardless of the stage,
- considered for all HIV-infected patients regardless of the stage, even if asymptomatic, because of the increased incidence of asymptomatic neurosyphilis in HIV-infected persons.

Diagnosis of neurosyphilis can be done by CSF findings of:

- confirmed with a positive VDRL in a non-bloody CSF specimen,
- presumptive for CSF total protein
- > 50-70 or CSF WBC > 10-20. ❖

A description of the 41 episodes of neurosyphilis from Ghanem's study

- 66% were symptomatic
 - most common symptom uveitis (33.3%)
 - other symptoms include: altered cognition (20.8%), motor weakness (16.7%), headache (12.1%), gait abnormality (9.0%), hearing loss (4.2%), and Bell's palsy (4.2%)
- 34% were asymptomatic
 - 57% evaluated for lack of response to therapy
 - 36% evaluated for a serum RPR > 1:32
 - median CD4 count was 331 cells/ml

	Median CD4 count	Serum RPR < 1:32	CSF WBC >10 WBC/microliter	CSF protein > 50 mg/dl	Positive CSF VDRL	All 3 abnormalities
Symptomatic 66%	189 cells/ml	16% (range 1:8 to 1:16)	69.6%	60.9%	79.2%	57.1%
Asymptomatic 34%	331 cells/ml	33% (range 1:2 to 1:16)	46.2%	58.3%	50%	8.3%

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