Published in final edited form as:

Sex Transm Dis. 2012 April ; 39(4): 298–299. doi:10.1097/OLQ.0b013e31824ee574.

Treponemal Tests for Neurosyphilis – Less Accurate Than What We Thought?

Emily L. Ho, MD, PhD and Christina M. Marra, MD

Treponema pallidum subsp. *pallidum* (hereafter termed *T. pallidum*) is the bacterium that causes syphilis. Neuroinvasion by *T. pallidum* occurs early in the course of disease (1-3) and can lead to asymptomatic meningitis that, untreated, can progress to symptomatic neurosyphilis. Early forms of symptomatic neurosyphilis include meningitis, hearing loss, vision loss, and stroke. Late forms include dementia (general paresis) and sensory ataxia (tabes dorsalis). Cerebrospinal fluid (CSF) analysis is crucial for diagnosis of asymptomatic and symptomatic neurosyphilis, but there is no perfect “gold standard” diagnostic test. Typical CSF abnormalities include mild mononuclear pleocytosis and elevated protein concentration. The CSF-Venereal Disease Research Laboratory (VDRL) test is specific but not sensitive, and particularly in early neurosyphilis, may be nonreactive. The “party line” has been that CSF treponemal antibody tests, while lacking the specificity of the CSF-VDRL, are diagnostically sensitive and can be used to rule out the diagnosis of neurosyphilis in equivocal cases.

A systematic review by Harding and Ghanem (4) published in this issue of *Sexually Transmitted Diseases* challenges this tenet. In their review, the authors assessed studies that described the performance of CSF treponemal tests. They focused on the negative predictive value of these tests and restricted the analysis to studies in which controls were individuals who had syphilis but not neurosyphilis, an approach that is most relevant to clinical practice. Perhaps not surprisingly for a disease that lacks a gold standard diagnostic test, the authors found that the sensitivity of the CSF treponemal tests varied with how neurosyphilis was defined. If CSF-VDRL reactivity was used to establish the diagnosis, the sensitivity of the CSF treponemal antibody tests consistently approached 100%, but if broader criteria were used, particularly including clinical manifestations, the sensitivity was lower and more variable (22.2%-100%).

Treponemal antibodies are directed against *T. pallidum* proteins, as detected by the fluorescent treponemal antibody absorbed (FTA-ABS) test, the *T. pallidum* particle agglutination (TPPA) test, the *T. pallidum* hemagglutination (TPHA) test or various enzyme immunoassays (EIAs). Another treponemal test included in the analysis, the microhemagglutination-*T. pallidum* (MHA-TP), is no longer commercially available. The FTA-ABS, TPPA and TPHA tests measure IgG and IgM antibodies to native *T. pallidum* antigens, while the EIA assays detect IgG and IgM antibodies to recombinant treponemal proteins, usually TpN15, TpN17, and TpN47. For the FTA-ABS, TPPA and TPHA tests, the patient's serum or CSF is mixed with sorbent to remove cross-reactive antibodies to non-pathogenic treponemes. CSF samples that are nonreactive by FTA-ABS test are often reactive when the absorption step is omitted (5). Because EIA does not require the pre-

Corresponding Author: Christina M. Marra, MD, Harborview Medical Center, Department of Neurology, Box 359775, 325 Ninth Ave., Seattle, WA 98104-2499, Telephone: 206-897-5400, Fax: 206-897-5401, cmarra@u.washington.edu.

Conflict of Interests: The authors declare there are no conflicts of interests.

absorption step, it could potentially be a more accurate test. However, there are no currently published studies using EIA on CSF to test this hypothesis.

In the studies analyzed by Harding and Ghanem, it is difficult to determine whether the treponemal antibodies measured in the CSF were made intrathecally or in the periphery. Some investigators have argued that CSF:serum treponemal antibody ratios or indices corrected for CSF and serum albumin or IgG concentrations can differentiate between intrathecal and peripheral antibody production and thus distinguish true CNS infection from passive diffusion of antibody from the peripheral blood (6-8). Sera from patients with reactive CSF FTA-ABS and CSF-TPPA tend to have higher treponemal antibody titers than sera from those with non-reactive tests, suggesting that a reactive CSF FTA-ABS or CSF-TPPA may simply be a surrogate for higher antibody concentration in sera (6, 9, 10). A study of the diagnostic utility of the CSF-TPHA suggested that a CSF titer >1:320 was as good as an elevated antibody index for neurosyphilis diagnosis (8), suggesting that there may be a CSF treponemal antibody concentration above which intrathecal antibody production is more likely. Distinguishing the source of CSF treponemal antibodies is important in assessing the accuracy of CSF treponemal tests. However, Harding and Ghanem did not include studies using such indices in their review.

Syphilis and HIV co-infection occurs commonly worldwide (11, 12). Diagnosing neurosyphilis in HIV-infected patients continues to be a challenge because HIV infection itself can cause CSF pleocytosis and elevated protein concentration. Only four of the studies (1, 3, 7, 13) assessed by the authors included HIV-infected patients, and one of the four studies had very small patient numbers (7), making it difficult for the authors to assess the accuracy of CSF treponemal tests in this patient population.

This article highlights the challenges clinicians caring for patients with syphilis continue to face – imperfect tests for neurosyphilis that are neither very sensitive nor specific. As the authors point out, while a positive CSF-VDRL “rules in” neurosyphilis, a negative CSF FTA-ABS does not necessarily “rule out” the diagnosis, especially when patients have neurological symptoms or signs. As the incidence of syphilis continues to increase, especially among HIV-infected patients, further work to develop better neurosyphilis diagnostic tests is sorely needed.

Acknowledgments

Sources of Support: The authors are supported by the National Institutes of Health

References

1. Lukehart SA, Hook EW, 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. [PubMed: 3056164]
2. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, Bolan G, Johnson SC, French P, Steen E, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*. 1997; 337:307–314. [PubMed: 9235493]
3. Marra CM, Maxwell CL, Smith SL, Lukehart SA, Rompalo AM, Eaton M, Stoner BP, Augenbraun M, Barker DE, Corbett JJ, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. 2004; 189:369–376. [PubMed: 14745693]
4. Harding AS, Ghanem KG. The Performance of Cerebrospinal Fluid Treponemal-Specific Antibody Tests in Neurosyphilis: A Systematic Review. *Sex Transm Dis*. in press.

5. Marra CM, Maxwell CL, Tantaló L, Eaton M, Rompalo AM, Raines C, Stoner BP, Corbett JJ, Augenbraun M, Zajackowski M, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. 2004; 38:1001–1006. [PubMed: 15034833]
6. Tomberlin MG, Holtom PD, Owens JL, Larsen RA. Evaluation of neurosyphilis in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 1994; 18:288–294. [PubMed: 8011805]
7. Marra CM, Critchlow CW, Hook EW 3rd, AC Collier, Lukehart SA. Cerebrospinal fluid treponemal antibodies in untreated early syphilis. *Arch Neurol*. 1995; 52:68–72. [PubMed: 7826278]
8. Luger AF, Schmidt BL, Kaulich M. Significance of laboratory findings for the diagnosis of neurosyphilis. *Int J STD AIDS*. 2000; 11:224–234. [PubMed: 10772085]
9. 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. [PubMed: 343742]
10. De Silva Y, Walzman M, Shahmanesh M. The value of serum TPHA titres in selecting patients for lumbar puncture. *Genitourin Med*. 1991; 67:37–40. [PubMed: 1916775]
11. Global prevalence and incidence of selected curable sexually transmitted infections: overview and estimates. Geneva: World Health Organization; 2001.
12. AIDS epidemic update: November 2009. Geneva: World Health Organization; 2009.
13. Castro R, Prieto ES, Aguas MJ, Manata MJ, Botas J, Araujo C, Borges F, Aldir I, Exposto Fda L. Evaluation of the *Treponema pallidum* particle agglutination technique (TP.PA) in the diagnosis of neurosyphilis. *J Clin Lab Anal*. 2006; 20:233–238. [PubMed: 17115423]