

Syphilis and HIV Co-Infection: When is Lumbar Puncture Indicated?

Derek J. Chan*

Albion Street Centre, 150-154 Albion Street, Surry Hills, Sydney, New South Wales 2010, Australia

Abstract: The rate of syphilis/HIV co-infection amongst men who have sex with men (MSM) in large urban regions ranges from 20 to 70% [7]. Concurrent HIV infection can alter the clinical presentation of syphilis, the response to treatment, and complicate the diagnosis and clinical course of neurosyphilis [18]. Therefore whether to perform a lumbar puncture (LP) on every co-infected patient in order to diagnose neurosyphilis is controversial. Current clinical guidelines specify the indications for LP, but fall short of recommending LP in certain clinical situations such as early syphilis without neurological involvement. This article reviews the current literature on the relative utility and indications for LP in syphilis/HIV co-infected patients and new research in this area.

SYPHILIS IN THE PRESENCE OF HIV INFECTION

The clinical features of syphilis are altered by concomitant HIV infection. HIV co-infection is associated with multiple chancres in primary syphilis and multiple concomitant genital ulcers in secondary syphilis [33], increased frequency of acute syphilitic meningitis in early syphilis [18], high rapid plasma reagin (RPR) titres, rapid progression to tertiary disease, increased ocular disease (uveitis, keratitis, optic neuritis, conjunctivitis, optic atrophy, chorioretinitis), delayed or failed normalisation of cerebrospinal fluid (CSF) markers after treatment, and predilection for the Jarisch-Herxheimer reaction [1, 6, 9, 13-15, 17, 19, 21, 29, 32, 36]. Further, syphilis can relapse following treatment in HIV-infected patients [1-3, 12, 13, 17, 19, 29, 30, 32, 35]. The pathogenesis of these clinical features may be related to the incomplete clearance of the spirochete from the central nervous system (CNS) because of relative immunodeficiency [22, 30]. Therefore, excluding neurosyphilis by CSF examination in co-infected patients becomes more important than in persons with syphilis alone.

Syphilis and the CNS

Before the advent of penicillin, examination of CSF by LP was performed routinely on patients with syphilis in order to determine the duration of heavy metal therapy [24]. Studies from the early part of the century showed CSF abnormalities such as pleocytosis and raised protein concentration in as many as 70% of patients with early syphilis [11, 26, 27, 31, 37] and, importantly, that these findings were predictive of the development of symptomatic neurosyphilis [28].

Treponema pallidum invades the CNS in approximately 25% of patients, irrespective of HIV sero-status [32]. Neuroinvasion occurs during untreated early syphilis, thence *T. pallidum* either **spontaneously clears** from the CNS, **persists** (asymptomatic syphilitic meningitis) or **progresses**

clinically (acute symptomatic syphilitic meningitis). Without treatment, persistent or progressive meningeal infection may develop into meningovascular syphilis (5-12 years after primary infection) or later forms of neurosyphilis such as tabes dorsalis (18-25 years). Why the spirochete demonstrates neurotropism is unclear, however recent animal studies implicate the *Borrelia Vsp-OspC* lipoproteins in neural tissue as facilitating CNS entry and avoidance of the host immune response by *T. pallidum* [38].

Diagnosing Neurosyphilis

A diagnosis of neurosyphilis depends on the integration of patient history, physical examination and laboratory tests such as syphilis serology and CSF examination. In surveillance terms, the disease prevalence is affected by the case definition used in individual jurisdictions, and this must be borne in mind when assessing prevalence estimates. Natural history studies indicate that neurosyphilis occurs in 4-9% of patients **without** HIV infection [15]. There is controversy whether neurosyphilis is commoner with concomitant HIV infection due to inconsistent neurosyphilis case definitions and clinical settings between studies. There are also inherent problems associated with interpreting CSF abnormalities (see below). In reality the prevalence of neurosyphilis in the HIV-infected population is unknown. For example, in San Francisco between 1985 and 1992, only 0.6% of all CSF-VDRL tests performed on 19,000 MSM with documented syphilis were reactive. Most of these men were HIV-infected [12]. Other studies set the prevalence of neurosyphilis at 1% in HIV clinic patients [14], 1.5% in AIDS patients [19], and as much as 7-16% when all HIV-infected patients are offered LP [14, 21, 32].

DIFFICULTIES INTERPRETING CSF FINDINGS

Laboratory diagnosis of neurosyphilis

In the appropriate clinical setting, CSF pleocytosis of > 5 cells/cm³ and a raised protein level are suggestive of neurosyphilis [6]. Unfortunately, HIV infection *per se* also produces pleocytosis and raised protein concentration that may be indistinguishable from that due to neurosyphilis [25]; however, a CSF pleocytosis of > 20 cells/mm³ is probably attributable to spirochete infection rather than HIV infection *per se* [8].

*Address correspondence to this author at the Albion Street Centre, 150-154 Albion Street, Surry Hills, Sydney, New South Wales 2010, Australia; Tel: (02) 9332.9600; Fax: (02) 9332.4219; E-mail: chander@sesahs.nsw.gov.au

A reactive CSF-VDRL titre confirms the diagnosis of neurosyphilis [6]. This is a highly specific test; however, active disease may still be present with a non-reactive CSF-VDRL titre [34]. In fact the sensitivity of the CSF-VDRL titre can be as low as 30% [39]. Also, false-positive CSF-VDRL titres occur in the presence of contamination from blood during a traumatic LP [36]. Despite its limitations, the CSF-VDRL remains the reference test for the laboratory diagnosis of neurosyphilis [6, 12].

Some specialists recommend performing a fluorescent treponemal antibody absorption test (FTA-ABS) on the CSF. The CSF FTA-ABS is less specific for neurosyphilis (i.e. yields more false-positive results) than the CSF-VDRL but it is more sensitive. Therefore, some specialists believe that a negative CSF FTA-ABS test excludes neurosyphilis [6].

The sensitivity and specificity of supplementary tests for neurosyphilis in patients *without* HIV infection have been evaluated, with a serological *T. pallidum* haemagglutination assay index > 70 and a CSF *T. pallidum* haemagglutination assay > 1:320 cited as the best tests to support a diagnosis of neurosyphilis [20]. Evaluation of test performance in HIV-infected patients with syphilis, however, is difficult because of the inherent problems with interpreting the CSF findings as discussed previously.

FACTORS AFFECTING NORMALISATION OF CSF MARKERS AFTER TREATMENT

Relative normalisation of CSF markers is affected by the stage of syphilis at which treatment is initiated [23] and CSF findings may persist following treatment for neurosyphilis [8]. Normalisation of CSF findings following treatment is also dependent on pre-treatment levels of particular CSF markers [23].

In most patients **without** HIV infection treated with standard neurosyphilis penicillin regimens [4-6], CSF pleocytosis and VDRL titre normalise within 1 year. Reversion of pleocytosis is more likely when pre-treatment CSF white cell counts are high. Conversely, CSF-VDRL normalisation is less likely when pre-treatment CSF-VDRL titres are high.

In **HIV-infected patients**, CSF white cell count, protein level and VDRL titre may be slow to normalise. [13, 23, 32]. CSF-VDRL titre is less likely to normalise following standard penicillin therapy, irrespective of pre-treatment CSF-VDRL titre and stage of syphilis at which neurosyphilis is diagnosed. In particular, CSF-VDRL titre is less likely to normalise when CD4+ count ≤ 200 cell/ μ L compared to CD4+ count > 200 cells/ μ L. Therefore in HIV-infected patients is not possible to exclude treatment failure and more intensive treatment regimens may be indicated [23].

LP IN CLINICAL PRACTICE

Indications

The CDC guidelines recommend CSF examination for patients presenting with:

- Neurologic or ophthalmic signs or symptoms;

- Evidence of active tertiary syphilis (e.g. aortitis, gumma, and iritis);
- Treatment failure; or
- HIV infection with late latent syphilis or syphilis of unknown duration (LP recommended before penicillin treatment).

The guidelines provide for LP in patients who do not meet these criteria, e.g. LP in all patients with latent syphilis and a non-treponemal serologic test of $\geq 1:32$. If a CSF examination is performed and the results indicate abnormalities consistent with neurosyphilis, treatment for neurosyphilis is recommended [6].

The European guidelines also recommend LP in patients presenting with tertiary symptoms or signs, neurological involvement and in the case of HIV co-infection, late latent syphilis or syphilis of unknown duration [10].

Assessing Response to Treatment

T. pallidum cannot be cultured directly from CSF, therefore successful treatment of neurosyphilis is indicated by normalisation (or stabilisation) of CSF markers such as white cell count, protein level and VDRL titre. CSF protein levels appear to fall slower and less completely than white cell count and VDRL titre, suggesting that CSF protein is less reliable as a marker for successful treatment of neurosyphilis [23]. A reactive CSF-VDRL titre may also be slow to normalise [13, 32] or remain reactive at a low level; however, a persistently reactive CSF-VDRL titre after therapy may be less important in assessing the response to treatment than the white cell count [6].

In order to gauge the success of treatment, current CDC guidelines require a decrease in white cell count by 6 months and normalisation of all CSF findings by 2 years. The magnitude of the decrease, however, is undefined. If CSF pleocytosis was present initially, a CSF examination is recommended every 6 months until the cell count is normal. If there is no decrease after 6 months, or if the CSF is not normal after 2 years, re-treatment should be considered [6].

The European guidelines recommend LP no earlier than 1-2 years after treatment for early syphilis and 2 years after treatment for neurosyphilis. CSF abnormalities detected by LP in an otherwise asymptomatic patient before these times are considered to be clinically irrelevant [10].

LP in Early Syphilis

Compared with HIV-negative patients, HIV-positive patients with early syphilis may be at increased risk for neurologic complications and higher rates of treatment failure with currently recommended penicillin regimens [6]. Therefore, should HIV-infected patients with primary, secondary and early latent syphilis **without** neurological symptoms or signs have LP performed routinely? If so, should one treat for neurosyphilis given that CSF findings and / or relative normalisation of same do not necessarily distinguish syphilis infection *per se* (whether active, spontaneously resolved or past-treated, depending on clinical context) from HIV infection *per se*?

Unlike patients with early syphilis only, the prognostic significance of pleocytosis and raised protein in HIV-infected

patients with early syphilis is unknown. Therefore, some specialists in the United States recommend CSF examination **before** treatment of HIV-infected persons with **early syphilis**, with follow-up CSF examination 6 months after treatment [6]. Early syphilis is not specified as an indication for LP in the European guidelines, but LP is recommended 2 years after treatment for early disease in HIV co-infected patients [10]. Others workers are more conservative and recommend LP in **all HIV-infected patients with any stage of syphilis** because of the (albeit undefined) risk of treatment failure or relapse following treatment [24].

LP on the Basis of Laboratory Parameters for Neurosyphilis

In a recent study, 65 patients with neurosyphilis underwent LP. 50 of these patients were co-infected with HIV. Independent risk factors for the development of neurosyphilis were a **plasma RPR \geq 1:32** (increased the risk of neurosyphilis by almost 6 times), or a **CD4+ count \leq 350 cells/ μ L** (increased the risk by 3 times). Patients with both parameters were 18 times more likely to develop neurosyphilis. These trends remained statistically significant after adjusting for previous syphilis therapy and stage of syphilis at time of LP [24]. Quantifying these laboratory risk factors may assist clinicians in selecting patients for LP. There are 2 possible ways this may happen.

The most conservative approach is to perform LP in all patients with plasma RPR \geq 1:32 and/or CD4+ count \leq 350 cells/ μ L these laboratory parameters at presentation [24]. The disadvantages of doing this are unnecessary LPs and over-treatment for neurosyphilis in patients who might otherwise spontaneously clear *T. pallidum* from the CNS; however, as discussed, it is impossible to predict which patients will clear the infection.

Alternatively, **LP may be deferred 6-12 months after treatment** for early syphilis and the criteria then applied to capture those patients at greatest risk for developing neurosyphilis [24]. In theory there would be less LPs and treatment at initial presentation, as plasma RPR (and thus risk of neurosyphilis) may have fallen by this time. The disadvantages of this approach include undetected and untreated neurosyphilis and loss of patients to follow-up.

CONCLUSION

HIV-infected patients are at increased risk for neurosyphilis and treatment failure and relapse, but the actual magnitude of this risk and prevalence of neurosyphilis in this population is unknown. Unfortunately, diagnosing neurosyphilis in HIV-infected patients is difficult because both syphilis and HIV infection of the CNS cause similar CSF abnormalities. Also, the CSF-VDRL does not always indicate whether neurosyphilis is actually present and white cell count and protein level do not reliably predict which patients will develop neurosyphilis. Following treatment for neurosyphilis, CSF markers do not necessarily indicate whether *T. pallidum* has been successfully eradicated.

Recent research shows that a plasma RPR \geq 1:32 and CD4+ count \leq 350 cells/ μ L are independent risk factors for

the development of neurosyphilis, suggesting that **the decision to perform LP based on clinical stage of syphilis alone is less satisfactory**. This finding is consistent with the hypothesis that HIV impedes the immunological clearance of *T. pallidum* from the CNS, particularly if there is a florid spirochetemia. As always, the risks and benefits of LP require discussion with the patient and informed consent obtained. Clinicians are now in a better position to assess the appropriateness of LP in patients co-infected with syphilis and HIV as a result of this research.

ABBREVIATIONS

AIDS	=	Acquired immunodeficiency syndrome
CNS	=	Central nervous system
CSF	=	Cerebrospinal fluid
FTA-ABS	=	Fluorescent treponemal antibody absorption test
HIV	=	Human immunodeficiency virus
LP	=	Lumbar puncture
MSM	=	Men who have sex with men
RPR	=	Rapid plasma reagin test
VDRL	=	Veneral diseases research laboratory test

REFERENCES

- [1] Berger JR, Waskin H, Pall L, Hensley G, Ihmedian I, Post MJ. (1992). *Neurology*. 7:1282-1287.
- [2] Berger JR. (1991). *Archives of Neurology*. 48:700-702.
- [3] Berry CD, Hooton TM, Collier AC, Lukehart SA. (1987). *New England Journal of Medicine*. 316:1587-1589.
- [4] Centers for Disease Control and Prevention. (1993). *Morbidity and Mortality Weekly Report*. 42:1-102.
- [5] Centers for Disease Control and Prevention. (1998). *Morbidity and Mortality Weekly Report*. 47:1-111.
- [6] Centers for Disease Control and Prevention. (2002). *Morbidity and Mortality Weekly Report*. 51:18-30.
- [7] Centers for Disease Control and Prevention. (2002). *Morbidity and Mortality Weekly Report*. 51:853-856.
- [8] Collier AC, Marra C, Coombs RW, Claypoole K, Cohen W, Longstreth WT Jr, Townes BD, Maravilla KR, Critchlow C, Murphy VL. (1992). *Journal of Acquired Immune Deficiency Syndromes*. 5:229-241.
- [9] Estanislao LB, Pachner AR. (1999). *Neurologic Clinics*. 17:783-800.
- [10] European Union Against Sexually Transmitted Infections. (2001). *International Journal of Sexually Transmitted Diseases and Acquired Immunodeficiency Syndrome*. 12(10):14-26.
- [11] Fildes P, Parnell RJ, Maitland HB. (1918). *Brain*. 41:255-301.
- [12] Flood JM, Weinstock HS, Guyroy ME, Bayne L, Simon RP, Bolan G. (1998). *Journal of Infectious Diseases*. 177:931-940.
- [13] Gordon SM, Eaton ME, George R, Larsen S, Lukehart SA, Kuypers J, Marra CM, Thompson S. (1994). *New England Journal of Medicine*. 331:1469-1473.
- [14] Holtom PD, Larsen RA, Leal ME, Leedom JM. (1992). *American Journal of Medicine*. 93(1):9-12.
- [15] Hook EW, Marra CM. (1992). *New England Journal of Medicine*. 326:1060-1069.
- [16] Gjestland T. The Oslo study of untreated syphilis. *Acta Dermatologica Venereologica* 1955;35(S34):11-36.
- [17] Horowitz HW, Valsamis MP, Wicher V, Abbruscato F, Larsen SA, Wormser GP, Wicher K. (1994). *New England Journal of Medicine*. 331:1488-1491.
- [18] Kassutto S, Sax PE. (2003). *Acquired Immunodeficiency Syndrome Clinical Care*. 15(2):9-15.

- [19] Katz DA, Berger JR, Duncan RC. (1993). Archives of Neurology. 50(3):243-249.
- [20] Luger AF, Schmidt BL, Kaulich M. (2000). International Journal of Sexually Transmitted Diseases and Acquired Immunodeficiency Syndrome. 11:224-234.
- [21] Malone JL, Wallace MR, Hendrick BB, LaRocco A Jr, Tonon E, Brodine SK, Bowler WA, Lavin BS, Hawkins RE, Oldfield EC 3rd. (1995). American Journal of Medicine. 99:55-63.
- [22] Marra CM, Longsteth WT, Maxwell CL, Lukehart SA. (1996). Sexually Transmitted Diseases. 23:184-189.
- [23] Marra CM, Maxwell CL, Tantalo L, Eaton M, Rompalo AM, Raines C. (2004). Clinical Infectious Diseases. 38:1001-1006.
- [24] Marra CM, Maxwell LM, Smith SL, Lukehart SA, Rompalo AM, Eaton M, Stoner BP, Augenbraum M, Barker DE, Corbett JJ, Zajackowski M, Raines C, Nerad J, Kee R, Barnett SH. (2004). Journal of Infectious Diseases. 189:369-376.
- [25] Marshall DW, Brey RL, Butzin CA, Lucey DR, Abbadessa SM, Boswell RN. (1991). Journal of Acquired Immune Deficiency Syndromes. 4:777-781.
- [26] Mills CH. (1927). British Medical Journal. 2:527-532.
- [27] Moore J. (1922) Bull Johns Hopkins Hospital. 33:231-246.
- [28] Moore JE, Hopkins H. (1930) Journal of the American Medical Association. 95:1637-1641.
- [29] Musher DM, Baughn RE. (1994). New England Journal of Medicine. 331:1516-1517.
- [30] Musher DM. (1991). Journal of Infectious Diseases. 163:201-206.
- [31] Ravaut P. (1903). Annales de Dermatologie et de Syphiligraphie 4:537-554.
- [32] Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, Bolan G, Johnson SC, French P, Steen E, Radolf JD, Larsen S. (1997). New England Journal of Medicine. 337:307-314.
- [33] Rompalo AM, Joesoef MR, O'Donnell JA, Augenbraun M, Brady W, Radolf JD, Johnson R, Rolfs RT. (2001). Sexually Transmitted Diseases. 28(3):158-165.
- [34] Ronald AR, Silverman M, McCutchan JA, Corey L, Handsfield HH. (1992). Clinical Infectious Diseases. 15(S2):S140-147.
- [35] Schofer H, Imhof M, Thoma-Greber E, Brockmeyer NH, Hartmann M, Gerken G, Pees HW, Rasokat H, Hartmann H, Sadri I, Emminger C, Stellbrink HJ, Baumgarten R, Plettenberg A. (1996). Genitourinary Medicine. 72:176-181.
- [36] Singh AE, Romanowski B. (1999). Clinical Microbiology Reviews. 12(2):187-209.
- [37] Wile UJ, Stokes JH. A study of the spinal fluid with reference to involvement of the nervous system in secondary syphilis. Journal of Cutaneous Diseases Including Syphilis. 1914;32:607-623.
- [38] Zuckert WR, Kerentseva TA, Lawson CL, Barbour AG. (2001). Journal of Biological Chemistry. 276(1):457-463.
- [39] Zunt HR, Marra CM. (1999). Neurologic Clinics. 17:675-689.

Received: 19 May, 2004

Accepted: 31 July, 2004