

ORIGINAL ARTICLES

Indications for Lumbar Puncture in Patients With Early Active Syphilis and Human Immunodeficiency Virus Coinfection: Experience in a Tertiary Level Hospital in La Coruña, Spain, 2003-2006

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Abstract. *Introduction:* In the last years, the incidence of syphilis has incremented in Spain and coinfection with HIV occurs in a high percentage. In HIV-infected patients with syphilis, neurological complications, treatment failure and relapse appear to be slightly raised. Therefore, careful follow-up must be carried out because of the risk of developing neurosyphilis. According to the guidelines, lumbar puncture (LP) is indicated in HIV-infected patients with late latent syphilis or syphilis of unknown duration, but it is discussed in HIV-infected patients with early active syphilis. Recent research has been developed in order to determine clinical and analytical findings for identification of patients with high neurosyphilis risk. We review different opinions about this topic and report our experience.

Methods. We have performed LP in all HIV-infected patients with early active syphilis during 2003-2006.

Results. Of the eight studied patients, none met criteria for neurosyphilis. Three of eight (38%) had a peripheral blood CD4 cell count $CD4 + \leq 350$ cells/ μ L. Seven of eight (87.5%) had RPR $\geq 1:32$.

Conclusion. In these patients, performance of LP could be over indicated because of lack of well-established criterion. Our results are in agreement over to recent studies which restrict indication of LP to specific groups.

Key words: syphilis, human immunodeficiency virus, lumbar puncture, neurosyphilis, venereal disease research laboratory test, rapid plasma reagin test.

INDICACIONES DE LA PUNCIÓN LUMBAR EN PACIENTES CON SÍFILIS PRECOZ ACTIVA COINFECTADOS POR EL VIH. CASUÍSTICA EN UN HOSPITAL TERCIARIO DE LA CORUÑA (ESPAÑA) 2003-2006

Resumen. *Introducción.* En los últimos años se ha incrementado la incidencia de sífilis en España. En un porcentaje importante existe coinfección con el virus de la inmunodeficiencia humana (VIH). Dado que estos pacientes tienen mayor riesgo de complicaciones neurológicas y de fracaso del tratamiento, hay que seguirlos cuidadosamente por el riesgo de desarrollar neurosífilis. En los pacientes coinfectados por el VIH –si bien las guías coinciden en realizar punción lumbar en aquellos con sífilis latente tardía o de duración incierta– la indicación en pacientes con sífilis precoz activa es controvertida. Recientemente se han realizado estudios para determinar parámetros clínicos o analíticos que identifiquen a aquellos pacientes que se beneficiarían de la punción lumbar. Exponemos las diversas opiniones y aportamos la experiencia en nuestro servicio.

Material y método. Hemos realizado punción lumbar de forma sistemática a todos los pacientes con sífilis precoz activa coinfectados por el VIH en el periodo 2003-2006.

Resultados. En el 100% no se objetivó neurosífilis en LCR, y los parámetros entraban dentro de la normalidad o eran compatibles con la infección por el VIH. Un 38% presentó un recuento de linfocitos $CD4 + \leq 350$ y un 87,5% tenía una titulación en suero RPR $\geq 1:32$.

Conclusión. Es posible que en la práctica clínica se abuse de la realización de PL en estos pacientes, debido a la ausencia de criterios bien definidos. Nuestros datos están en correlación con los criterios actuales que apoyan la idea de restringir la realización de PL a determinados grupos.

Palabras clave: sífilis, VIH, punción lumbar, neurosífilis, VDRL, RPR.

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Introduction

With highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) infection is now considered a chronic disease. The false sense of security regarding HIV infection has been cited as the cause of the increasing incidence of syphilis and other sexually transmitted diseases, particularly among men who have sex with other men and even in populations with stable HIV infection rates.¹⁻⁴

Although syphilis may still follow an atypical course (more aggressive and less responsive to treatment) in patients with HIV infection, thanks to HAART, the disease now develops in a similar manner in patients with and without infection.^{5,6}

One aspect that needs to be elucidated in the management of syphilis in patients with HIV infection is whether or not to perform lumbar puncture to exclude asymptomatic neurosyphilis. The dramatic increase in syphilis incidence detected in recent years in Spain and other western countries^{4,7-14} has heightened interest in establishing clear guidelines for action in such cases.

We present our experience with systematic lumbar puncture performed over 4 years in patients with primary or secondary syphilis of less than a year's duration at a tertiary care hospital in La Coruña, Spain.

Material and Methods

Between January 2003 and December 2006, we performed a lumbar puncture in every patient with HIV infection and early syphilis (primary or secondary syphilis of less than a year's duration) treated by the dermatology department at

Complejo Hospitalario Universitario Juan Canalejo, La Coruña, Spain.

All the patients underwent physical examination including a neurologic examination. Patients with visual signs or symptoms also underwent an ophthalmologic examination with a slit lamp.

Laboratory and other tests were ordered in accordance with clinical findings and in all cases included a complete blood count, white blood cell (WBC) differential count, erythrocyte sedimentation rate, routine biochemistry, a protein profile, rapid plasma reagin (RPR), fluorescent treponemal antibody absorption (FTA-ABS), HIV, and CD4⁺ cell counts in peripheral blood.

Analysis of cerebrospinal fluid (CSF) included evaluation of glucose, proteins, white and red blood cells, Venereal Disease Research Laboratory (VDRL) titers, and Gram staining and culture for bacteria, mycobacteria, and fungi.

Diagnosis of neurosyphilis was based on a pleocytosis of greater than 20 WBC/mm³ or a positive CSF-VDRL test.^{6,15}

Results

We performed a lumbar puncture in 8 patients with syphilis and HIV infection between 2003 and 2006. They all had secondary syphilis and the results of the neurologic examination were unremarkable. None of them had visual or auditory signs or symptoms.

The diagnostic criteria for neurosyphilis were not met in any of the patients and the CSF findings were within normal ranges or consistent with HIV infection. Four patients (50%) had a CD4⁺ count of $\leq 350/L$ and 7 (87.5%) had a serum RPR titer of $\geq 1:32$ (Table 1).

Table 1. Clinical and Laboratory Data for Patients Studied

Patient	Sex	Age, y	Clinical Stage	VDRL Titers	CSF			Peripheral Blood
					WBC/mm ³	FTA-ABS	RPR	CD4 ⁺ Count
1	M	41	Secondary syphilis	–	3	–	1/256	613
2	M	52	Secondary syphilis	–	3	–	1/64	337
3	M	50	Secondary syphilis	–	0	–	1/16	360
4	M	43	Secondary syphilis	–	0	–	1/32	70
5	M	43	Secondary syphilis	–	0	–	1/256	237
6	M	44	Secondary syphilis	–	5	–	1/64	171
7	M	41	Secondary syphilis	–	2	–	1/128	428
8	M	41	Secondary syphilis	–	14	–	1/256	401

Abbreviations: CSF, cerebrospinal fluid; FTA-ABS, fluorescent treponemal antibody absorption; M, male; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; WBC, white blood cells.

Table 2. Indications for Lumbar Puncture According to the Centers for Disease Control and Prevention (CDC) Guidelines for 2002 and 2006^{18,21}

Neurologic/ophthalmic signs
Late syphilis
Treatment failure
Patient with HIV infection and late latent syphilis or syphilis of unknown duration

The 2002 CDC guidelines mention that some specialists recommend lumbar puncture in patients with latent syphilis and a serum RPR titer of $\geq 1:32$ and the 2006 guidelines state that this is now also an option in patients with HIV infection and a CD4+ count of $\leq 350/L$. Abbreviation: HIV, human immunodeficiency virus.

Discussion

In early syphilis, *Treponema pallidum* invades the central nervous system (CNS) in 25% to 60% of cases. Although the reason for this neurotropism is still unknown, it has been suggested that *Borrelia* Vsp-OspC lipoproteins in natural tissues might be involved as they facilitate *pallidum* invasion of the CNS without triggering an immune response.⁶

Once in the CNS, *T pallidum* may be cleared spontaneously, persist (causing asymptomatic meningitis), or develop clinically (causing acute symptomatic meningitis). If left untreated, the infection can develop into meningovascular syphilis within 5 to 12 years, and into later forms of syphilis such as tabes dorsalis, general paralysis, or gummatous syphilis within 18 to 25 years.

Between 4% and 9% of patients with untreated syphilis without HIV infection syphilis develop neurosyphilis.^{6,16} The corresponding percentage in patients with HIV infection is not known but it has been demonstrated that HIV infection facilitates invasion of the CNS by *T pallidum* and vice versa.¹⁷ If we also consider that *T pallidum* is not entirely cleared from the CNS in immunocompromised patients, the greater concern to rule out neurosyphilis (by analyzing CSF) in patients with HIV infection is understandable.

Diagnosis of neurosyphilis is based on consideration of clinical history, physical examination, and CSF findings. It is well known that both HIV and neurosyphilis can cause pleocytosis and increased CSF protein levels. HIV infection, however, tends to produce mild pleocytosis and this is why a WBC count of over 20 cells/mm³ is highly suggestive of neurosyphilis.^{6,17}

The CSF-VDRL test has high specificity,¹⁸ which is why it is routinely used in the diagnosis of neurosyphilis, but it also has low sensitivity (30%).¹⁹ In other words, a positive result will confirm disease but a negative one will not rule it out. It is also important to bear in mind that blood in the

CSF caused by a traumatic lumbar puncture may cause a false positive.

Some specialists recommend performing an FTA-ABS test because of its high negative predictive value¹⁸ (a negative result would rule out neurosyphilis). While hemagglutination tests are useful for diagnosing neurosyphilis, they are not recommended for patients with HIV infection as interpretation can be difficult.^{6,20}

The indications for treating neurosyphilis are clear but there is a lack of consensus regarding lumbar puncture, particularly where patients with HIV coinfection are concerned.

In the 1980s and 1990s, there were many reports of cases involving patients with early syphilis and HIV infection who, despite receiving appropriate treatment, developed neurosyphilis within weeks and in some cases even months of treatment. There were no such reports, however, in patients without HIV infection. Since then, many experts have recommended performing lumbar puncture in all patients with HIV coinfection but this opinion is not shared by all.

The latest guidelines from the Centers for Disease Control and Prevention (CDC), issued in 2002¹⁸ and 2006²¹ (Table 2), recommend lumbar puncture in patients with HIV infection and late latent syphilis or latent syphilis of unknown duration.

Although the 2001 European guideline for the management of syphilis coincides with the CDC's recommendation of performing lumbar puncture in patients with CNS disease and late syphilis, it also recommends that this procedure be performed 2 years after treating patients with early syphilis and HIV infection.²²

Whether or not lumbar puncture should be performed in patients with HIV infection and early syphilis is therefore the subject of continuous debate. While some physicians will never perform this procedure in the absence of clinical suspicion of neurosyphilis, others will do so 2 years after treating early syphilis. Both options carry the risk of the patient dying and of neurosyphilis going undetected and therefore untreated. Experts with a more conservative approach prefer to perform systematic lumbar puncture in patients with syphilis and HIV infection before initiating treatment and some even recommend repeating the procedure periodically.^{6,18}

Several studies have been conducted in search of clinical and analytical parameters that might help to identify patients with an increased risk of neurosyphilis²³⁻²⁵ as it is these patients, and particularly those with latent syphilis, who would benefit most from lumbar puncture.

As has already been mentioned, the CDC does not indicate lumbar puncture for patients with HIV infection and early syphilis, arguing that the clinical and prognostic significance of the CSF abnormalities seen in these patients is unknown, that reactive VDRL tests during early syphilis

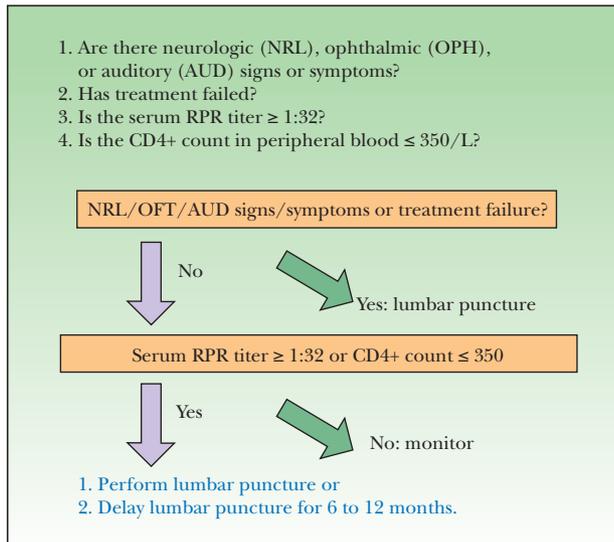


Figure. How to proceed with a patient with early syphilis and human immunodeficiency virus infection.^{6,18,21,24,25} RPR indicates rapid plasma reagin.

become nonreactive without specific treatment for neurosyphilis, and that more cases would have been detected if there were considerable neurologic involvement.

To date, however, there has been no evidence that a reactive CSF-VDRL test is any less suggestive of neurosyphilis in a patient with early syphilis than in one with late latent syphilis or syphilis of unknown duration. The true incidence of neurosyphilis is unknown because it is not a notifiable disease and because lumbar puncture is not performed in many cases.²⁵

It was recently demonstrated that patients coinfecting with syphilis and HIV, regardless of disease stage or history of previous treatment, had a 6-fold increased risk of developing neurosyphilis if they had a serum RPR titer of $\geq 1:32$ ^{24,25} and a 3-fold increased risk if they had a peripheral blood CD4+ count of $\leq 350/L$. These are independent factors, so if they coincide, the risk increases by 18.²⁴

Accordingly, if lumbar puncture is only performed in patients with HIV infection and late latent syphilis or syphilis of unknown duration, we will be neglecting patients with a high risk of neurosyphilis (those with HIV infection and early syphilis and a serum RPR titer of $\geq 1:32$ or a CD4+ count of $\leq 350/L$) and performing unnecessary tests in patients with a low risk (those with HIV infection and late latent syphilis or syphilis of unknown duration and a serum RPR titer of $\leq 1:32$ or a CD4+ count of $\geq 350/L$).^{24,26}

In the absence of clearly defined criteria on when lumbar puncture might be indicated in patients with HIV and early syphilis infection, we believe that the procedure has been overindicated to date.

Our findings support the idea that lumbar puncture should be limited to patients with relevant risk as it is an

invasive test that carries risk and requires expertise. Nausea, ringing in the ears, and persistent headache have been reported in 37% of patients who have undergone lumbar puncture.²⁷

Because HAART has changed the course of HIV infection and syphilis in coinfecting patients, and in view of recent findings,^{24,25} it would seem logical to only perform lumbar puncture in patients with poor immune response and massive spirochetemia, and not to base decisions on clinical disease stage or HIV positivity, as has been the case to date (Figure).

Author's note. We have followed the patients from when this article was accepted to date and none of them have developed neurologic signs or symptoms.

Conflicts of Interest

The authors declare no conflicts of interest.

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