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Evaluation of Treponemal Serum Tests Performed on Cerebrospinal Fluid for Diagnosis of Neurosyphilis

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Abstract

Objectives—We evaluated the use of treponemal serum tests in cerebrospinal fluid (CSF) to diagnose neurosyphilis since CSF–Venereal Disease Research Laboratory (VDRL) is specific but lacks sensitivity.

Methods—We tested CSF specimens using the following treponemal serum tests: INNO-LIA, Treponema pallidum particle agglutination (TP-PA), Trep-Sure, and Maxi-Syph. The reference standard to calculate sensitivity and specificity was having two or more reactive/positive tests on CSF.

Results—The reference standard group included 11 cases that fulfilled the definition of neurosyphilis (reactive CSF-VDRL plus symptoms) and three cases that did not fulfill the definition: two cases had neurologic symptoms but a nonreactive CSF-VDRL, and one had several positive CSF syphilis tests (reactive VDRL and positive treponemal and syphilis polymerase chain reaction) but no history (referred sample). Controls included 18 patients in whom a CSF-VDRL was performed the same week as patients in the reference group. The sensitivity was 85.7% (12/14) for CSF-VDRL, 92.9% (13/14) for Trep-Sure, 100% (10/10) for Maxi-Syph, 92.3% (12/13) for INNO-LIA, and 83.3% (10/12) for TP-PA. Specificity was 100% for all tests.

Conclusions—Treponemal serum tests performed on CSF were useful in identifying two patients with nonreactive CSF-VDRL.

Keywords

Neurosyphilis; Treponemal tests; VDRL; Cerebrospinal fluid

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Clinical diagnosis of neurosyphilis is challenging since patient presentation varies. Persons with clinical signs of neurosyphilis (eg, cranial nerve dysfunction, auditory or ophthalmic abnormalities, loss of vibration sense, altered mental status, meningitis, and stroke) warrant further laboratory investigation. Although no single laboratory test can be used to diagnose neurosyphilis, a variety of laboratory parameters in cerebrospinal fluid (CSF) can aid in the diagnosis, yet there are caveats in different patient groups[1] and those coinfected with human immunodeficiency virus (HIV).[2] A definitive diagnosis of neurosyphilis can be performed by identifying *Treponema pallidum* in CSF by polymerase chain reaction (PCR), detecting treponemes in brain tissue by silver staining, immunohistochemistry, or direct fluorescent antiNormal, but these test modalities and samples are not available in many clinical settings.

In a person with neurologic signs or symptoms, a reactive CSF–Venereal Disease Research Laboratory (VDRL) (in a specimen not contaminated with blood) is considered diagnostic of neurosyphilis, while probable cases include patients with clinical signs suggestive of neurosyphilis or suggestive of other syphilis stages with negative CSF-VDRL but reactive serologic treponemal and nontreponemal tests and alterations in the CSF protein or leukocyte counts.[3] Because the CSF-VDRL test has high specificity but lacks sensitivity,[4] serum *T pallidum*–specific or treponemal tests such as *T pallidum* particle agglutination (TP-PA) or fluorescent treponemal antiNormal absorption (FTA-ABS) have been used to test CSF to improve neurosyphilis diagnosis.[5-9] However, TP-PA and FTA-ABS are manual tests performed in reference laboratories, and their use in serum has been supplanted by treponemal enzyme immunosorbent assays (EIAs) and chemiluminescent immunoassays (CIAs), which are automated and interfaced to electronic medical records.[10] When using serum, the agreement of treponemal EIAs and CIAs with FTA-ABS is above 95%.[11] Added advantages of using automated instrumentation to detect treponemal-specific antibodies on CSF specimens include requiring low specimen volume and quick turnaround time. The goal of this study was to evaluate the use of serum treponemal immunoassays on CSF specimens and define their potential use for diagnosis of neurosyphilis.

Materials and Methods

Specimen Selection

Twelve VDRL-positive CSF specimens were collected from January 2011 to May 2013 after routine testing had been completed in one laboratory from a two-hospital system. One or two VDRL-negative CSF specimens that were tested in the same laboratory during the same week when a CSF-VDRL–positive sample occurred were included as controls. CSF specimens were refrigerated prior to batch testing with VDRL and subsequently frozen at −20°C. Except for the CSF-VDRL test, all other syphilis tests were performed at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, with spent CSF samples (remaining sample after other diagnostic tests were performed), and thus the volume varied and not all tests could be performed in some cases.

Chart Review

Patients' charts were reviewed and the following information was extracted: age; sex; neurologic signs and symptoms; rapid plasma reagin (RPR) test result; HIV status, including

CD4 cell count; and viral load when available. We also captured specific treatment for neurosyphilis with intravenous penicillin. Completeness of clinical information varied since some specimens were referred by other institutions. The study protocol was reviewed and approved by institutional review boards at Emory University and the CDC.

Tests Performed on CSF

The VDRL test was performed according to the manufacturer's instructions (Becton-Dickinson, Sparks, MD). Reactive specimens were titered by preparing twofold dilutions of each sample. The CSF-VDRL test is a nontreponemal test that measures antilipid (mostly cardiolipin) antibodies that appear as a result of *T pallidum* infection.

The Trep-Sure (Trinity Biotech, Bray, Ireland) and Maxi-Syph (Sire Diagnostics, Oakville, Ontario, Canada) EIAs were performed according to the manufacturers' instructions. Both tests use a microtiter plate coated with highly purified specific *T pallidum* antigen and measure both IgG and IgM antitreponemal antibodies. EIA plates were read on a FLUOstar Omega microplate reader (BMG Labtech, Ortenburg, Germany). Results were reported based on the serum sample's index value, which was calculated by dividing the sample's optical density by the cutoff value. A specimen was considered nonreactive if the index value was less than 0.8 and reactive if more than 1.2, while in-between values were considered equivocal.

The INNO-LIA Syphilis Score test was performed using the AUTO-LIA 48 automated system according to the manufacturer's instructions (Innogenetics N.V., Gent, Belgium). INNO-LIA is a line immunoassay that tests for IgG and IgM antibodies against specific treponemal antigens, three recombinant proteins (TpN47, TpN17, and TpN15), and a synthetic peptide (TmpA). Samples and controls are placed on the paper strip containing the antigens. Detection of an antigen/antiNormal reaction is done by using an enzymatic reaction. A specimen is considered positive if reactivity is observed with at least two of the four antigens.

The Serodia–TP-PA test (Fujirebio America, Fairfield, NJ) was performed according to the manufacturer's instructions. Gelatin particles coated with purified *T pallidum* organisms will agglutinate with anti–*T pallidum* antibodies in a patient's serum, indicating the presence of IgG and IgM antitreponemal antibodies.

DNA was extracted from 200 μL and 400 μL for each patient's CSF sample per the manufacturer's instructions using the QIAamp DNA mini kit (Qiagen, Valencia, CA). Both DNA samples were eluted for a total volume of 50 μL. DNA samples were tested with real-time duplex PCR targeting the DNA polymerase I gene (*polA*, *tp0105*) of *T pallidum* and a PCR inhibition control targeting the human ribonuclease P gene. PCR amplification was performed in a 50-μL reaction using 20 μL of the DNA sample. The PCR reaction mixture contained 300 nmol/L sense primer (CAGGATCCGGCATATGTCC), 300 nmol/L antisense primer (AAGTGTGAGCGTCTCATCATTCC), and 200 nmol/L TaqMan probe (CalRed610-CTGTCATGCAC-CAGCTTCGACGTCTT–black hole quencher 3 [BHQ3]) for *polA* detection, as well as 80 nmol/L sense primer (CCAAGTGTGAGGGCTGAAAAG), 80 nmol/L antisense primer (TGTTGTGGCTGATGAACTATAAAAGG), and 80 nmol/L

TaqMan probe (Cy5-CCCCA GTCTCTGTCAG-CACTCCCTTC-BHQ3) for human ribonuclease P gene detection; 1× PCR buffer; 5 mmol/L $MgCl_2$; 200 μmol/L each dATP, dGTP, dCTP, and dUTP; 1 unit of uracil-*N*-gly-cosylase; and 2 units of AmpliTaq Gold DNA polymerase (Applied Biosystems, Carlsbad, CA). Appropriate positive- and negative-template controls were included in the run. PCR amplification was done in a Rotor-Gene 6000 real-time PCR instrument (Qiagen, Germantown, MD) using the following conditions: hold cycles at 50°C for 2 minutes and 95°C for 10 minutes, followed by 50 PCR cycles at 95°C for 20 seconds and 60°C for 1 minute.

As part of the patients' diagnostic workup, CSF cellularity, protein and glucose concentration, and tests to rule out other causes of meningitis or encephalitis were performed on CSF specimens from these patients.

Statistical Analysis

To calculate sensitivity, specificity, and positive and negative predictive values, we divided patients into two groups; those who had two or more reactive/positive treponemal, nontreponemal, or PCR tests in CSF were considered the reference (gold) standard, while other patients were considered controls. Comparison of these two groups for age and CSF values regarding cellularity and glucose and protein concentration was performed using a two-tailed, unpaired *t* test using the online QuickCalks (GraphPad Software, La Jolla, CA).

Results

A total of 32 CSF specimens were tested. The mean age of the patients was 50 years, including 10 women and 22 men. Thirty patients had neurologic signs and symptoms. Patients without neurologic symptoms included a 53-year-old HIV-positive man who had a fever and a sample from a 49-year-old man who was referred for testing. Of the 30 symptomatic patients, 12 had HIV infection; 10 of 12 patients had a CD4 cell count available at the time the CSF specimen was obtained, with a mean CD4 cell count of 268 (range, 8-642). In three of the 12 HIV-infected patients, a viral load was available; it was less than 20 in one patient, and the other two had uncontrolled viremia (>57,000). Two HIV-infected persons had hepatitis C.

Fourteen of 32 patients were considered in the reference group; 11 fulfilled the definition of having neurosyphilis, while three did not. The cases that did not fulfill the definition included a 41-year-old man with neurologic symptoms (decreased hearing, tinnitus, and loss of vision) and a positive RPR but negative CSF-VDRL. A 49-year-old man whose specimen was referred for testing (no clinical information was available) had a reactive CSF-VDRL, positive treponemal tests in CSF, and a positive PCR in CSF. The last patient in the gray zone was a 50-year-old HIV-positive woman who had altered mental status, nausea, vomiting, and diarrhea; did not have a serum RPR performed, although she had increased CSF protein and lymphocytes; and was diagnosed as having a stroke. This patient had antisyphilis antibodies detected by the serum tests in CSF, suggesting that she had syphilis, particularly since she frequented the emergency department but refused care.

The mean age for the reference group was 43 (range, 25-56) years, and the mean age for the control group was 53 (range, 18-89) years ($P = .037$). **Table 1** presents in aggregate the clinical and laboratory characteristics of patients in the reference and control groups. The diagnoses of the 18 controls included neoplasias, stroke, autoimmune disease (multiple sclerosis), suspected viral encephalitis, and diabetes with encephalopathy. RPR was performed on serum in 10 of the 14 patients in the reference group and in five of 18 controls. The serum RPR was reactive with titers ranging from 1:32 to 1:512 in nine patients in the reference group. The patient with the reactive serum RPR in the control group had a titer of 1:4 and was considered as having a false-positive result since an enzyme-linked immunosorbent assay syphilis antiNormal test was negative in the setting of a stroke (nonreactive CSF-VDRL and no CSF WBCs).

Appropriate treatment for neurosyphilis with intravenous penicillin was documented in 10 of the 14 patients in the reference group. For those patients in whom treatment of neurosyphilis was not documented, one was referred to his primary care physician for treatment, and two patients were noncompliant with treatment; the last treatment is unknown since the CSF specimen was a referral. None of the patients in the control group were treated for syphilis or neurosyphilis.

Patients in the reference group had lower CSF glucose (54 mg/dL; range, 36-66 mg/dL) compared with controls (mean, 76 mg/dL; range, 53-175 mg/dL) ($P = .029$) and higher protein (mean, 99 mg/dL; range, 35-300 mg/dL) compared with controls (mean, 42 mg/dL; range, 18-100 mg/dL) ($P = .025$). The increased WBC count became statistically significant between the groups ($P < .05$) once the patient with carcinomatosis was excluded (since all cells present in CSF were malignant rather than inflammatory). The mean number of white blood cells was 17/μL (range, 0-76/μL) in the reference group and 3/μL (range, 0-27/μL) the control group. In the reference group, 12 (92%) of 13 patients had a predominance of lymphocytes in CSF, while this occurred in only eight (57%) of 14 controls. None of the CSF specimens was bloody.

Table 2 shows the results of syphilis tests performed on CSF from both groups. CSF-VDRL was reactive in 12 (85.7%) of 14 patients in the reference group, with titers ranging from 1:1 to 1:32. None of the patients in the control group had a positive CSF-VDRL test. Trep-Sure was performed on all 32 specimens, INNO-LIA on 31, TP-PA on 30, and Maxi-Syph on 28. Of the 14 patients in the reference group, 13 CSF samples tested positive by Trep-Sure, including two patients who were CSF-VDRL nonreactive; 10 of 12 tested were positive by TP-PA; 12 of 13 by INNO-LIA; 10 of 10 by Maxi-Syph; and 2 of 10 by PCR. Reextraction and concentration of DNA from CSF did not yield any additional positives by PCR.

Of the two patients with nonreactive VDRL but reactive Trep-Sure specimens, one was the 41-year-old HIV-positive man with possible neurosyphilis who had tinnitus and loss of vision and also had reactive CSF with TP-PA, INNO-LIA, and Maxi-Syph. The other patient was a 50-year-old woman with HIV infection who had a cerebrovascular accident and whose CSF tested positive by the Maxi-Syph EIA.

The CSF-VDRL missed two patients in the reference group, giving a sensitivity of 85.7% a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 89.5%. One patient in the reference group tested negative by Trep-Sure EIA, giving a test sensitivity of 92.9%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 94.7%. All 10 samples tested were reactive by the Maxi-Syph EIA, giving 100% sensitivity, specificity, and positive and negative predictive values. As with Trep-Sure, INNO-LIA missed one patient in the reference group, giving a sensitivity of 92.3%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 94.7%. The TP-PA missed two patients in the reference group, giving a sensitivity of 83.3%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 90%.

Discussion

Our results indicate that Trep-Sure, Maxi-Syph EIA, TP-PA, and INNO-LIA performed on CSF could be useful for the diagnosis of neurosyphilis when the CSF-VDRL is nonreactive, which is particularly problematic in patients with asymptomatic neurosyphilis who are coinfected with HIV.[2,3,12,13] In our evaluation, there were three probable cases of neurosyphilis, including two HIV-positive patients with negative CSF-VDRL. One patient had decreased hearing, tinnitus, and loss of vision, and all treponemal tests on CSF were positive, while the other patient had altered mental status and a cerebrovascular event with only positive EIA treponemal tests on CSF. Our data suggest that it may be useful to perform treponemal tests in CSF of HIV-positive patients when the CSF-VDRL is nonreactive but neurosyphilis is suspected.

Treponemal tests performed on CSF showed good sensitivity and specificity in our study. Previous studies using treponemal tests on CSF specimens have primarily used FTA, FTA-ABS, TP-PA, and a *T pallidum* hemagglutination assay.[14-19] A systematic review of these publications showed that the performance was difficult to assess due to the heterogeneity of the populations tested and the methods used to assess diagnosis.[20] Recently, INNO-LIA has been used in CSF specimens, although the authors advocate the use of an IgG and IgM serum CSF index to define central nervous system involvement.[19,21] It should be noted that when serum CSF indexes are proposed for diagnoses of a variety of conditions, obtaining the serum specimen may be neglected, leading to lack of usage of these indexes. Publications regarding performance and use of Trep-Sure and the INNO-LIA assay are available for serum, showing good sensitivity and specificity.[11,21-24]

Consideration should be given to the possibility of the passage of antisyphilis IgG antibodies from serum to CSF when using serum treponemal tests for the evaluation of CSF infection.[25] Although we did not address this question, one of the patients in the reference group had a negative CSF-VDRL with a reactive RPR of 1:128, lymphocytic pleocytosis, and reactive treponemal tests, which likely indicate central nervous system involvement; however, a breach in the blood-brain barrier cannot be ruled out. On the other hand, one could argue that if treponemal tests in CSF are positive because of the passage of antibodies through the blood-brain barrier, both cases in this series with nonreactive CSF-VDRL should be considered to have possible neurosyphilis.

PCR positivity in our study was lower than the 25% to 60% range reported in other studies.[9,25,26] Reported sensitivity for PCR performed in swabs of primary and secondary syphilitic lesions is 82%, with a specificity of 95%, compared with dark-field microscopy. When performing PCR on plasma or serum, the sensitivity decreases to around 16% and is lower in the later stages of syphilis, suggesting there are few treponemes circulating in peripheral blood.[27] Freeze-drying CSF concentrates the sample and improves PCR sensitivity.[25] Currently, the utility of CSF PCR to detect *T pallidum* is not well established since the presence of DNA does not necessarily indicate disease activity but the residual presence of nucleic acids.[28] The low PCR-positive rate observed in our study can be attributed to using CSF specimens that had been refrigerated rather than frozen immediately.

There are several limitations to this study. Clinical information was retrospective, and control group specimens were selected randomly so not all clinical parameters were available. Not all tests could be performed in each sample because we used spent samples and the volume varied. Last, the conformation of the reference group requiring two or more reactive/positive treponemal, nontreponemal, or PCR CSF tests likely increased the calculation of sensitivity and specificity. Of the patients included in the reference group, the 50-year-old HIV-positive woman with a stroke was the only patient who could be considered in either group. We elected to place her in the reference group because she had antibodies against syphilis in CSF, which likely reflect the presence of antibodies in serum, particularly in a patient who frequently refused care.

In summary, our study shows that serum treponemal tests performed on CSF may be useful to diagnose neurosyphilis where there is high clinical suspicion but the CSF-VDRL is nonreactive. The advantages of EIA platforms (Trep-Sure and Maxi-Syph) include the presence of instruments that can perform the tests in most clinical laboratories and technologists' familiarity with EIAs; however, validation of the sample type will need to be conducted in each laboratory. Although our results are preliminary due to the small sample size, they support the use of an algorithm in which serum treponemal tests are performed in CSF specimens once clinicians communicate with the laboratory that the CSF-VDRL was nonreactive but the patient has signs and symptoms compatible with neurosyphilis.

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Table 1

Clinical Information and Pertinent Laboratory Test Results of Reference and Control Groups[a]

Characteristic	Reference Group (n = 14)[b]	Control Group (n = 18)
Age, mean (range), y	43 (25-56)	53 (18-89)
Male sex	13 (93)	9 (50)
Symptoms		
Headache	5 (38)	5 (28)
Visual disturbances	5 (38)	3 (17)
Psychological disturbances	4 (31)	2 (11)
Nausea, vomiting	4 (31)	3 (17)
Dizziness	2 (15)	2 (11)
Hearing problems	1 (8)	1 (6)
Gait abnormalities	1 (8)	3 (17)
Sleeping disturbances	1 (8)	1 (6)
Fever	1 (8)	2 (11)
No neurologic symptoms	1 (8)	0
Numbness, paresthesias	0	4 (22)
Focal neurologic signs	0	2 (11)
Tremors	0	1 (6)
Increased intracranial pressure	0	1 (6)
Reactive RPR, No. performed	9 of 10	1 of 5
Range of RPR titer	1:32 to 1:512	1:4
HIV positive, No. performed	11 of 12	1 of 4

HIV, human immunodeficiency virus; RPR, rapid plasma reagin.

[a] Values are presented as number (%) unless otherwise indicated.

[b] No clinical information is available in one specimen in the reference group since it was referred for testing.

Table 2

Syphilis Serology and PCR Testing on CSF Specimens of Reference and Control Groups

Age, y/Sex	VDRL	Trep-Sure	Maxi-Syph	TP-PA	INNO-LIA	PCR
Reference group						
35/M	R	R	ND	ND	ND	ND
43/M	R	R	ND	ND	R	ND
47/M	R	R	R	R	R	−
33/M	R	R	R	R	R	+
49/M	R	NR	R	NR	R	+
56/M	R	R	R	R	R	−
32/M	R	R	R	R	R	−
55/M	R	R	R	R	R	−
53/M	R	R	R	R	R	−
52/M	R	R	ND	R	R	−
31/M	R	R	ND	R	R	ND
25/M	R	R	R	R	R	−
41/M	NR	R	R	R	R	−
50/F	NR	R	R	NR	NR	−
Control group						
47/F	NR	NR	NR	NR	NR	−
65/F	NR	NR	NR	NR	NR	−
57/M	NR	NR	NR	NR	NR	−
51/F	NR	NR	NR	NR	NR	−
89/F	NR	NR	NR	NR	NR	−
19/F	NR	NR	NR	NR	NR	−
58/F	NR	NR	NR	NR	NR	−
70/M	NR	NR	NR	NR	NR	−
88/M	NR	NR	NR	NR	NR	−
44/M	NR	NR	NR	NR	NR	−
40/M	NR	NR	NR	NR	NR	−
48/M	NR	NR	NR	NR	NR	−
18/M	NR	NR	NR	NR	NR	−
57/F	NR	NR	NR	NR	NR	−
54/F	NR	NR	NR	NR	NR	−
63/M	NR	NR	NR	NR	NR	−
85/F	NR	NR	NR	NR	NR	−
60/M	NR	NR	NR	NR	NR	−

CSF, cerebrospinal fluid; ND, not done; NR, nonreactive; PCR, polymerase chain reaction; R, reactive; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory; +, positive; −, negative.