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The Rapid Plasma Reagin Test Cannot Replace the Venereal Disease Research Laboratory Test for Neurosyphilis Diagnosis

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Abstract

Background—The cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) test is a mainstay for neurosyphilis diagnosis, but it lacks diagnostic sensitivity and is logistically complicated. The Rapid Plasma Reagin (RPR) test is easier to perform, but its appropriateness for use on CSF is controversial.

Methods—RPR reactivity was determined for CSF from 149 individuals with syphilis using two methods. The CSF-RPR was performed according to the method for serum. The CSF RPR-V was performed using the method recommended for the CSF-VDRL. Laboratory defined neurosyphilis included reactive CSF-Fluorescent Treponemal Antibody Absorption test and CSF white blood cells > 20/ul. Symptomatic neurosyphilis was defined as vision loss or hearing loss.

Results—CSF-VDRL was reactive in 45 (30.2%) patients. Of these, 29 (64.4%) were CSF-RPR reactive and 37 (82.2%) were CSF-RPR-V reactive. There were no instances where the CSF VDRL was nonreactive but the CSF-RPR or CSF-RPR-V was reactive. Among the 28 samples that were reactive in all three tests, CSF-VDRL titers (median [IQR], 1:4 [1:4–1:16]) were significantly higher than CSF-RPR (1:2 [1:1–1:4], $p=0.0002$) and CSF-RPR-V titers (1:4 [1:2–60 1:8], $p=0.01$). The CSF RPR and the CSF-RPR-V tests had lower sensitivities than the CSF VDRL: 56.4% and 59.0% vs. 71.8% for laboratory-diagnosed neurosyphilis and 51.5% and 57.6% vs. 66.7% for symptomatic neurosyphilis.

Conclusions—Compared to the CSF-VDRL, the CSF-RPR has a high false-negative rate, thus not improving upon this known limitation of the CSF-VDRL for neurosyphilis diagnosis. Adapting the RPR procedure to mimic the CSF-VDRL decreased, but did not eliminate, the number of false negatives, and did not avoid all the logistical complications of the CSF VDRL.

Keywords

syphilis; neurosyphilis; diagnosis; Venereal Disease Research Laboratory test; Rapid Plasma Reagin test; cerebrospinal fluid

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Introduction

The nontreponemal cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) test is a mainstay for diagnosis of neurosyphilis. Although the estimated specificity of the test is high, the sensitivity is lower, which is a major limitation of the test (1). The method for both the serum and CSF-VDRL tests require specialized glass plates and a light microscope. The CSF version of the test differs from that for serum: the cardiolipin-lecithin cholesterol antigen is diluted and a smaller volume of the antigen suspension is used, which adjust for the much lower concentration of immunoglobulin in CSF compared to blood (2), and the diluted antigen can be used only for two hours after it is prepared (3). In contrast to the VDRL test, the Rapid Plasma Reagin (RPR) test for plasma or serum incorporates carbon particles, which enables the test to be performed on a disposable paper card and read with the naked eye, rather than a microscope. The serum Toluidine Red Unheated Serum Test (TRUST) is the same as the RPR test except that paint particles are used instead of carbon particles (4).

There is little published experience on using the RPR or TRUST to detect nontreponemal antibodies in CSF. Larsen and coworkers assessed RPR and TRUST reactivity in 1063 CSFs including 10 samples from individuals with late symptomatic neurosyphilis, 10 samples from persons with asymptomatic neurosyphilis defined as elevated CSF WBC and protein concentrations, 50 samples from patients with other stages of syphilis, most of whom had been treated, and 993 samples from individuals with other neurological diseases (the controls) (1). They concluded that the CSF-RPR and CSF-TRUST were “totally unsatisfactory” for diagnosis of neurosyphilis because, while all control CSF-VDRLs were nonreactive, 139 (14%) of the controls were CSF-RPR and CSF-TRUST reactive. The estimated diagnostic sensitivity and specificity of the CSF-RPR/CSF-TRUST for neurosyphilis was 40% and 85.2% compared to 50% and 99.8% for the CSF-VDRL.

Castro and colleagues assessed CSF-RPR reactivity in 314 CSF samples, including 24 from patients with neurosyphilis defined as serum RPR titer 1:8, serum Microhemagglutination Assay for *Treponema pallidum* (MHATP) titer 1:80, reactive CSF-Fluorescent Treponemal Antibody Absorption (FTA-ABS) test, and elevated CSF WBC or CSF protein concentrations; 163 samples from patients with other forms of syphilis, including 61 patients who had been treated; and 126 controls with other neurological diseases (5). In contrast to the experience of Larsen and coworkers (1), CSF-VDRL and CSF-RPR were reactive in only one control. The estimated diagnostic sensitivity and specificity of the CSF-RPR, 75.0% and 99.3%, was higher than in the Larsen study (1).

Most recently, Jiang and colleagues retrospectively assessed CSF-TRUST reactivity in 75 patients with syphilis, 41 of whom had neurosyphilis defined as CSF WBCs > 5/ul with a reactive CSF-*Treponema pallidum* particle agglutination assay test (6). The estimated diagnostic sensitivity and specificity of the CSF-TRUST for neurosyphilis was 94.7% and 100.0% compared to 93.1% and 100.0% for the CSF-VDRL. The authors concluded that the CSF-TRUST could be used in place of the CSF-VDRL.

The purpose of our study was to further clarify whether the CSF-RPR could serve as a potential point-of-care test for neurosyphilis diagnosis that could replace the CSF-VDRL and whether adapting the CSF-RPR to be performed according to the protocol for the CSF VDRL might improve its diagnostic performance.

Materials and Methods

Study Participants

One hundred forty-nine patients who were enrolled in a study of CSF abnormalities in patients with syphilis conducted in Seattle, WA (7) are included in this report. Individuals were eligible for enrollment if they had clinical or serological evidence of syphilis, and were assessed by the referring provider as possibly having neurosyphilis. Reasons for referral to the study included 1) neurological findings, particularly hearing loss or visual loss; 2) serum RPR titer 1:32, and 3) in HIV-infected individuals, peripheral blood CD4+ T cell count 350/ul. The latter criteria are based on published data (7-9). All participants underwent a structured history and neurological examination that included assessment of cranial nerves, motor strength, sensation, coordination, reflexes and gait; lumbar puncture; and venipuncture. Participants included in this study represent a convenience sample selected to over-represent asymptomatic and symptomatic neurosyphilis.

The study protocol was reviewed and approved by the University of Washington Institutional Review Board, and human experimentation guidelines were followed in the conduct of this research. Written informed consent was obtained from all participants.

Laboratory Methods

Serum RPR and CSF-VDRL tests were performed according to standard methods (3). The RPR antigen and control sera, and the VDRL antigen and VDRL buffered saline were manufactured by Becton-Dickinson (Franklin Lakes, NJ). FTA-ABS kits were manufactured by Inverness Medical Professional Diagnostics (Princeton, NJ). Cerebrospinal fluid-FTA ABS reactivity was determined using the method specified for serum substituting cell-free CSF for serum (3). Cerebrospinal fluid RPR tests were performed using two methods: 1) according to the standard method for serum but substituting cell-free CSF for serum; and 2) modified to be similar to the CSF-VDRL method. Specifically, the CSF-VDRL method is modified from that recommended for sera to adjust for the lower concentration of immunoglobulin in CSF relative to serum. Accordingly, we diluted commercial RPR antigen 1:2 in 10% saline and allowed it to stand for 5 minutes before use, as is done with the VDRL antigen when it is used with CSF. We also used the lower volume of antigen that is specified for the CSF-VDRL test. Hereafter, we use the terms CSF-RPR to refer to method #1 and CSF RPR-V to refer to method #2. For each patient tested, CSF-VDRL, CSF-RPR and CSF-RPR-V reactivity was determined on the same thawed CSF aliquot on the same day by the same operator who was blinded to the patient's clinical status. Measurement of CSF red blood cell (RBC) and white blood cell (WBC) concentrations was performed in a CLIA-approved clinical laboratory. Median CSF RBC (IQR) was 1/ul (0-9), and 164 the highest WBC concentration was 600/ul. Detection of *T. pallidum* in CSF by reverse transcriptase polymerase chain reaction (RT-PCR) was performed using a published method (7).

Statistical Methods

Patients with laboratory-defined neurosyphilis had reactive CSF-FTA-ABS and CSF WBCs > 20/ul and were compared to those with nonreactive CSF-FTA-ABS and CSF WBCs ≤ 20/ul, regardless of clinical findings. Patients with symptomatic neurosyphilis had vision loss or hearing loss and were compared to those without vision or hearing loss, regardless of CSF abnormalities. CSF-VDRL and CSF-RPR titers, using either method, were log base 2 transformed for direct comparison using t-tests. Comparison of median values between groups was performed using Mann-Whitney U test, and comparison of proportions was performed using chi-square or Fisher's exact tests. Specificity, sensitivity and kappa values were calculated using standard formulae. Two sided p values <0.05 were considered to be statistically significant. No adjustments were made for multiple comparisons.

Results

Participant Characteristics

The characteristics of study participants are shown in Table 1. Most were HIV-infected men, reflecting the demographics of syphilis in Seattle. Thirty-nine individuals had laboratory-defined neurosyphilis (31 [79.5%] HIV-infected) and 33 had vision or hearing loss (24 [72.7%] HIV-infected); 18 patients (13 [72.2%] HIV-infected) met both definitions.

CSF-VDRL, CSF-RPR and CSF-RPR-V Test Results

Cerebrospinal fluid (CSF) VDRL tests were reactive in 45 patients. As shown in Figure 1, there were no instances in which the CSF-VDRL was nonreactive but the CSF-RPR or CSF RPR-V was reactive. Of the 45 samples that were reactive by CSF-VDRL, 29 were reactive by CSF-RPR and 37 were reactive by CSF-RPR-V, likely reflecting a more optimal antigen antibody ratio as a result of diluting the RPR antigen and using a smaller amount of antigen for the CSF-RPR-V. One sample was reactive by CSF-RPR but nonreactive by CSF-RPR-V, and 9 samples were reactive by CSF-RPR-V but nonreactive by CSF-RPR. Agreement between results of the CSF-VDRL and the CSF-RPR was good ($\kappa=0.72$), and agreement between the results of the CSF-VDRL and the CSF-RPR-V was very good ($\kappa=0.87$). Among the 28 samples that were reactive in all three tests, CSF-VDRL titers (median [IQR], 1:4 [1:4-1:16]) were significantly higher than CSF-RPR titers (1:2 [1:1-1:4], $p=0.0002$) and CSF-RPR-V titers (1:4 [1:2-1:8], $p=0.01$), but CSF-RPR and CSF-RPR-V titers were not significantly different from each other ($p=0.12$).

Table 2 shows differences between patients whose CSFs were reactive by CSF-VDRL and CSF-RPR compared to those whose CSF-VDRL was reactive but CSF-RPR was nonreactive. In general, patients whose CSF-VDRL and CSF-RPR were both reactive had greater CSF abnormalities, higher serum RPR titers and were more likely to have vision and hearing loss than patients whose CSF-VDRL was reactive but CSF-RPR was nonreactive. These differences were statistically significant for CSF WBCs and bordered on significance for vision and hearing loss. There were no statistically significant differences between patients whose CSF samples were reactive by CSF-VDRL and CSF-RPR-V and whose CSF samples were reactive by CSF-VDRL but nonreactive by CSF-RPR-V, although the analysis was limited by the small number of the discordant patients ($n=8$).

Table 3 shows the sensitivity and specificity of each of the three CSF serological tests for diagnosis of laboratory-defined and symptomatic neurosyphilis. For laboratory-defined neurosyphilis, the specificity of the three tests was virtually identical. For symptomatic neurosyphilis, the CSF-RPR was significantly more specific than the CSF-VDRL ($p=0.04$). For both definitions of neurosyphilis, the CSF-RPR and CSF-RPR-V tests had lower sensitivities than the CSF-VDRL, reflecting a greater number of false negative results (Figure 1). Nonetheless, the differences in sensitivity of the tests were not statistically significant. However, when the WBC cut-off for asymptomatic neurosyphilis was lowered to $>10/\mu\text{l}$, rather than $>20/\mu\text{l}$ as in our original definition, the sensitivity of the CSF-RPR was significantly lower than the CSF-VDRL (51.0% [37.0-65.0] vs. 71.4% [58.7-84.1], $p=0.04$), but did not differ significantly between the CSF-RPR-V and the CSF-VDRL (59.2% [45.4-73.0] vs. 71.4%, [58.7-84.1] $p=0.20$).

Discussion

A reactive CSF-VDRL is diagnostic of neurosyphilis, and the CSF-VDRL is generally considered to be the “gold standard” test. However, the CSF-VDRL test method is technically cumbersome. It requires specialized equipment including a light microscope, and the antigen for the test can only be used for two hours, after which it must be remade.

Although one study reported in 1986 suggested that the CSF-RPR and CSF-TRUST tests, which are less logistically complicated to perform than the CSF-VDRL test, should not be used to diagnose neurosyphilis (1), two more recent studies suggested that the CSF-RPR or CSF-TRUST could be suitable alternatives to the CSF-VDRL, reporting specificities close to 100% for laboratory-defined neurosyphilis (5, 6). We also found that the CSF-RPR performed using the method recommended for serum or adapted to reflect the method used for the CSF-VDRL (CSF-RPR-V) was highly specific for the diagnosis of laboratory defined neurosyphilis. Specificity was lower for all three CSF nontreponemal tests for diagnosis of symptomatic neurosyphilis. Nonetheless, the specificity of the CSF-RPR for diagnosis of symptomatic disease was significantly better than the CSF-VDRL.

At first glance, our data might be construed as supporting use of the CSF-RPR as a replacement for the CSF-VDRL. However, several of our additional findings should temper this conclusion. The fact that the CSF-RPR is significantly more specific than the CSF-VDRL means that it is more likely to be negative than the CSF-VDRL in a patient without neurosyphilis. This finding is striking from a statistical perspective, but is it clinically relevant? False positive CSF-VDRL results are uncommon, and usually reflect blood contamination of CSF (10); they don't represent a major clinical problem. On the other hand, a chief drawback of the CSF-VDRL is its lack of diagnostic sensitivity. In our study, the CSF-VDRL had 71.8% sensitivity for diagnosis of laboratory-defined neurosyphilis, and 80.2% sensitivity for diagnosis of symptomatic neurosyphilis. We found that, compared to the CSF-VDRL, the CSF-RPR was falsely negative in 35.6% of cases and the CSF-RPR-V was falsely negative in 17.8% of cases. This high rate of false-negatives is reflected in their lower diagnostic sensitivities for laboratory-diagnosed and symptomatic neurosyphilis. While the sensitivities of the CSF-VDRL and the RPR tests on CSF did not differ significantly, from a clinical perspective, the differences we observed are impressive. Were we to advocate replacing the CSF-VDRL with the CSF-RPR or CSF-RPR-V, we would be suggesting beginning with a test (the CSF-VDRL) that suffers from false negatives and replacing it with a test that, compared to the CSF-VDRL, is additionally falsely negative approximately one fifth to one-third of the time.

In our study, there were twice as many false-negatives with the CSF-RPR compared to the CSF-RPR-V. The CSF-RPR was more likely to be falsely negative when there was less meningeal inflammation as reflected by lower CSF WBC concentrations. The nontreponemal tests depend on formation of complexes between the cardiolipin-lecithin cholesterol antigen and IgG and IgM; formation is dependent on an optimal ratio of the components. The concentrations of IgG and IgM in CSF are roughly 1000-fold less than in serum (2). It is thus likely that this ratio was suboptimal for the CSF-RPR, explaining the higher false negative rate and the dependence of a positive result on greater CSF inflammation. However, even when the antigen was diluted and a smaller volume used for the CSF-RPR-V test, as is done for the CSF-VDRL, there were still false negatives, and both CSF-RPR and CSF-RPR-V titers were significantly lower than CSF-VDRL titers. This difference is notable because it is the opposite of what is generally seen in serum, where the RPR titer for a given serum specimen may be 2-4 times greater than the VDRL titer (4). Thus it is likely that modification of the CSF-RPR to mimic the CSF-VDRL was not sufficient to completely optimize the test.

Our study should be interpreted in the context of similar research. We found no instances where the CSF-VDRL was nonreactive but the CSF-RPR or CSF-RPR-V was reactive. In contrast, Larsen and colleagues identified one (16.7%) of six patients with secondary syphilis and 12 (27.2%) of 44 patients with treated syphilis (1) and Castro identified three (12.5%) of 24 patients with asymptomatic or symptomatic neurosyphilis (5) who had a nonreactive CSF-VDRL but a reactive CSF-RPR. Our rate of false negative CSF-RPR (16

(35.6%) of 45) was similar to that identified by Larsen and colleagues (2 (20.0%) of 10), but greater than that identified by Castro and colleagues (1 (5.8%) of 17). Our study benefited from a larger number of patients with neurosyphilis than these previous studies. In addition, in our study, all three CSF nontreponemal tests were performed on the same sample on the same day by the same observer, which may have decreased the variability of test results.

Our study has limitations that should be considered in interpretation of our results. In contrast to other studies, most of our CSF samples were from patients who were also infected with HIV. It is possible, although unproven, that HIV-infected patients have impaired antibody responses to the antigen used in the VDRL and RPR tests on CSF. However, there is no reason to think that HIV would differentially impact the results of the individual assays, which use the same antigen. Moreover, the sensitivity and specificity of the CSF-VDRL for diagnosis of neurosyphilis in this study is comparable to that described in HIV-uninfected individuals (1). Our definition of laboratory-defined neurosyphilis included patients who did and did not have neurological symptoms, and our definition of symptomatic neurosyphilis included individuals who did and did not have CSF abnormalities. However, repeating our analyses restricting the definition of laboratory defined neurosyphilis to those without vision or hearing loss and restricting the definition of symptomatic neurosyphilis to those who also had a reactive CSF-FTA-ABS test and CSF WBCs > 20/ul did not alter our conclusions regarding the sensitivities of the three tests (data not shown).

Estimates of sensitivity and specificity of diagnostic tests will vary based on the definition of the gold standard. Our results exemplify this fact. While the sensitivity of the RPR tests on CSF for laboratory-defined neurosyphilis did not differ significantly from the CSF-VDRL when the gold standard was reactive CSF-FTA-ABS and CSF WBCs > 20/ul, the diagnostic sensitivity of the CSF-RPR was significantly worse than that of the CSF-VDRL when the gold standard was revised to include a reactive CSF-FTA-ABS and CSF WBCs > 10/ul. The important finding of this study, and one that is independent of the definitions of neurosyphilis, is that the CSF-RPR had a high false-negative rate, providing no improvement on this known limitation of the CSF-VDRL. Adapting the RPR procedure to mimic the CSF-VDRL decreased, but did not eliminate, the number of false negatives, and did not avoid all the logistical complications of the CSF-VDRL. Future work should focus on developing a dedicated and accurate CSF point-of-care neurosyphilis diagnostic test. Until then, clinicians should be aware that the VDRL test is more accurate than the RPR test for detection of nontreponemal antibodies in CSF.

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Summary

Comparison between the cerebrospinal fluid (CSF)-Venereal Disease Research Laboratory (VDRL) and CSF-Rapid Plasma Reagin tests found that CSF RPR tests yielded false negative results compared to the CSF-VDRL.

Figure 1.

Results of CSF serological tests. Forty-five of 149 CSFs were CSF-VDRL reactive. There were no instances in which the CSF-VDRL was nonreactive but the CSF-RPR or CSF RPR-V was reactive. Of the 45 samples that were reactive by CSF-VDRL, 29 were reactive by CSF-RPR and 37 were reactive by CSF-RPR-V. One sample was reactive by CSF-RPR but nonreactive by CSF-RPR-V, and 9 samples were reactive by CSF-RPR-V but nonreactive by CSF-RPR. Twenty-eight samples were reactive in all three tests.

Table 1

Characteristics of Study Participants

Characteristic or Value	Number (Percent) or Median (IQR)		
	All (n=149)	Laboratory-defined Neurosyphilis (n=39)	Symptomatic Neurosyphilis (n=33)
Male	145 (97.3%)	38 (97.4%)	31 (93.9%)
Age, yrs	37 (32-43)	37 (30-44)	38 (32-44)
HIV-infected	124 (83.2%)	31 (79.5%)	24 (72.7%)
Syphilis Stage			
Early	99 (66.4%)	26 (66.7%)	20 (60.6%)
Late	50 (33.6%)	13 (33.3%)	13 (39.4%)
1/Serum RPR titer	64 (16-256)	256 (128-512)	256 (64-512)
Reactive CSF-FTA-ABS (n=148)	69 (46.6%)	39 (100.0%)	24 (72.7%)
CSF WBCs > 20/ul	58 (38.9%)	39 (100.0%)	20 (60.6%)
Identification of <i>T. pallidum</i> in CSF by RT-PCR (n=148)	30 (20.3%)	17 (43.6%)	12 (36.4%)

Patients with laboratory-defined neurosyphilis had reactive CSF-FTA-ABS and CSF WBCs > 20/ul. Patients with symptomatic neurosyphilis had vision loss or hearing loss.

Table 2

Laboratory and Clinical Characteristics of Patients with Reactive CSF-VDRL and Reactive CSF-RPR Compared to those with Reactive CSF-VDRL and Nonreactive CSF-RPR

Characteristic or Value	Median (IQR) or Number (Percent)		P-value
	CSF-VDRL+ and CSF-RPR+ (n=29)	CSF-VDRL+ and CSF-RPR- (n=16)	
CSF WBC/ul	76 (22-139)	20 (6-38)	0.005
CSF Protein mg/dl	61 (52.5-90.5)	63.5 (46.5-81.3)	0.34
Identification of <i>T. pallidum</i> in CSF by RT-PCR	13 (46.4%) (n=28)	5 (31.3%)	0.33
1/Serum RPR titer	256 (96-512)	192 (80-256)	0.18
Laboratory-defined Neurosyphilis	22 (100.0%) (n=22)	6 (85.7%) (n=7)	0.24
Symptomatic Neurosyphilis	17 (58.6%)	5 (31.3%)	0.08

Patients with laboratory-defined neurosyphilis had reactive CSF-FTA-ABS and CSF WBCs > 20/ul. Patients with symptomatic neurosyphilis had vision loss or hearing loss.

Table 3

Sensitivity and Specificity of the Three CSF Nontreponemal Serological Tests for Diagnosis of Neurosyphilis

	Diagnostic Criterion			
	Laboratory-Defined Neurosyphilis (n=99)		Symptomatic Neurosyphilis (n=149)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)*
CSF-VDRL	71.8 (57.7-85.9)	98.3 (95.0-100.0)	66.7 (50.6-82.8)	80.2 (72.9-87.5)
CSF-RPR	56.4 (40.8-72.0)	100.0 (100.0-100.0)	51.5 (34.4-68.6)	89.7 (84.2-95.2)
CSF-RPR-V	59.0 (43.6-74.4)	98.3 (95.0-100.0)	57.6 (40.7-74.5)	84.5 (77.9-91.1)

Patients with laboratory-defined neurosyphilis had reactive CSF-FTA-ABS and CSF WBCs > 20/ul. Patients with symptomatic neurosyphilis had vision loss or hearing loss.

* For diagnosis of symptomatic neurosyphilis, the CSF-RPR was significantly more specific than the CSF-VDRL (p=0.04).