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MAJOR ARTICLE

HIV Testing in Adults Presenting With Central Nervous System Infections

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Background. Universal HIV testing in adults presenting to a health care setting was recommended by the Centers for Disease Control and Prevention (CDC) in 2006, but compliance in central nervous system (CNS) infections is unknown.

Methods. A multicenter study of adults presenting with CNS infections to 18 hospitals in Houston and New Orleans between 2000 and 2015 was done to characterize HIV testing and explore factors associated with a positive HIV test.

Results. A total of 1478 patients with a diagnosis of meningitis or encephalitis were identified; 180 were excluded because of known HIV diagnosis (n = 100) or were <17 years old (n = 80). Out of 1292 patients, 642 (49.7%) had HIV testing, and testing did not differ significantly before or after the CDC recommendations in 2006 (53% vs 48%; $P = .068$). An HIV test was more commonly done in patients who were non-Caucasian, had fever >38°C, or had seizures on presentation, and of those tested, non-Caucasian patients and those with photophobia were more likely to have a positive HIV test ($P < .05$). HIV testing also varied by type of CNS infection: community-acquired bacterial meningitis (98/130, 75.4%), encephalitis (174/255, 68.2%), aseptic meningitis (285/619, 46.0%), and health care–associated meningitis (85/288, 29.5%; $P < .001$).

Conclusions. Even though HIV testing should be done in all adults presenting with a CNS infection, testing remains ~50% and did not improve after the recommendation for universal testing by the CDC in 2006.

Keywords. aseptic meningitis; bacterial meningitis; CNS infection; encephalitis; HIV.

Currently, over 1.1 million people in the United States are living with HIV, with 15% unaware of their infection. Each year ~38700 new Americans become infected [1, 2]. Increased testing is 1 of the 4 pillars to target ending the HIV epidemic. Since 2006, the Centers for Disease Control and Prevention (CDC) recommends a 1-time universal HIV screening of patients aged 13 to 64 while in a health care setting and repeat screening based on risk factors [3]. Before universal HIV screening recommendations, the CDC recommended HIV testing in individuals who presented with an HIV-associated illnesses. This change from HIV testing based on the patient's illness to a universal screen removes the providers' need to decide if a patient has an illness that would require an HIV test.

Current testing uses fourth-generation enzyme-linked immune absorbent assay (ELISA), which detects both p24 antigen and HIV antibodies, which allows for earlier HIV detection during acute stages [4]. In patients suspected of having earlier acute HIV seroconversion syndrome, HIV RNA polymerase chain reaction (PCR) can be used to detect the virus weeks before regular testing methods would detect HIV antibodies or proteins [4–7]. Despite the increase in availability of HIV screening methods, less than half (46%) of the nonelderly adults in the United States have been screened for HIV in their lifetime [1, 2].

Underutilization of HIV testing in CNS infections can potentially result in misdiagnoses and/or delayed treatment, as knowing the HIV status can impact the differential diagnosis of a particular patient. During initial HIV infection, patients can present with acute HIV seroconversion syndrome [8]. These symptoms include fevers, lethargy, nausea, myalgia, and headaches and can be mistaken for meningitis or encephalitis [9, 10]. Moreover, patients with HIV infection can also present with mild neurocognitive symptoms such as problems with memory, difficulty concentrating, and distal sensory neuropathy [11]. Patients living with HIV can also present with a wide variety of opportunistic CNS infections such as cryptococcal meningitis, cytomegalovirus encephalitis, or progressive multifocal leukoencephalopathy [12, 13].

Few studies have evaluated HIV testing in patients with a CNS infection. The purpose of our study was to assess the prevalence and factors associated with HIV testing in adults with CNS infections and to identify predictors for a positive HIV test.

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Table 1. Baseline Characteristics of 1292 Patients With Meningitis or Encephalitis by HIV Testing and Results

Variable	HIV Test Not Performed (n = 650) No. (%)		HIV Test Performed (n = 642) No. (%)		*P**	HIV Test Negative (n = 566) No. (%)		HIV Test Positive (n = 76) No. (%)		*P***
Demographics										
Female	334/650	(51)	305/642	(48)	.163	268/566	(47)	38/76	(50)	.644
Caucasian race	413/642	(64)	266/600	(44)	.000	242/525	(46)	24/75	(32)	.022
Years 2000–2006[a]	218/464	(47)	246/464	(53)	.068	189/246	(33)	57/246	(23)	.000
Years 2007–2015	432/828	(52)	396/828	(48)		377/396	(95)	19/396	(5)	
History										
Fever >38°C	163/445	(37)	254/564	(45)	.007	218/488	(45)	36/76	(47)	.660
Focal neurologic abnormalities	74/545	(14)	53/458	(12)	.341	48/387	(12)	5/71	(7)	.194
Glasgow Coma Scale score <15	219/646	(34)	201/640	(31)	.340	190/564	(34)	11/76	(14)	.001
Headache	449/570	(79)	426/570	(75)	.107	365/496	(74)	61/74	(82)	.102
Nausea	312/580	(54)	306/596	(51)	.400	266/522	(51)	40/74	(54)	.618
Nuchal rigidity	130/530	(25)	122/512	(24)	.792	103/439	(23)	19/73	(26)	.634
Otitis	17/610	(3)	18/548	(3)	.621	17/460	(4)	1/73	(1)	.326
Photophobia	157/516	(30)	181/556	(33)	.454	144/483	(30)	37/73	(51)	.000
Seizures	45/631	(7)	108/631	(17)	.000	104/555	(19)	4/76	(5)	.003
Sinusitis	24/605	(4)	47/549	(9)	.001	37/476	(8)	10/73	(7)	.090
Type of CNS infection										
Aseptic meningitis[b]	334/619	(54)	285/619	(46)	.000	232/285	(81)	53/285	(19)	.000
Encephalitis	81/255	(32)	174/255	(68)		167/174	(96)	7/174	(4)	
Health care–associated meningitis	203/288	(70)	85/288	(30)		85/85	(100)	0/85	(0)	
Community-acquired bacterial meningitis	32/130	(25)	98/130	(75)		82/98	(84)	16/98	(16)	

Abbreviation: CNS, central nervous system.

*P value for comparing results between patients with and without HIV test requested; **P value for results between patients with positive and negative HIV tests.

[a]Case occurred from 2000 to 2006.

[b]Only 8 patients with aseptic meningitis had an HIV RNA polymerase chain reaction performed to rule out acute HIV seroconversion syndrome; all 8 results were negative.

METHODS

Study Design and Case Definition

We performed a multicenter retrospective study of patients over the age of 17 years with community- or health care–associated bacterial meningitis, aseptic meningitis, or encephalitis admitted to 18 hospitals in New Orleans, Louisiana, and Houston, Texas, from January 1, 2000, through December 31, 2015. The case definitions used for the 4 types of CNS infections for this study have been published recently [14–18]. The study was approved by the Tulane University Institutional Review Board, the University of Texas Health Committee for the Protection of Human Subjects, and the Memorial Hermann Hospital System in Houston, Texas. Patients were identified using ICD-9 coding and by screening cerebrospinal fluid (CSF) analysis logs from the hospitals. Patients were excluded if they had previously been diagnosed with HIV or were under the age of 17 years.

Data Collection and Parameter Definitions

Electronic medical records of identified patients were reviewed. Baseline clinical characteristics such as demographic data, concurrent conditions (determined by Charlson Comorbidity Index), immunologic status, clinical features (including neurologic examination findings and Glasgow Coma Scale score), and laboratory test results were recorded when the patient presented in the emergency department. Aseptic meningitis cases were also reviewed for HIV RNA PCR testing in order to determine acute HIV seroconversion status [2, 14, 15]. Lymphocytic pleocytosis was defined as total CSF leukocyte composition >50% lymphocytes.

HIV Testing and HIV RNA PCR

HIV status testing was performed by ELISA. Some of the patients with aseptic meningitis were also tested for acute HIV seroconversion status using HIV RNA PCR. Acute HIV seroconversion syndrome was defined as a positive HIV RNA PCR test with a positive ELISA with a negative antibody immunoassay.

Statistical Analysis

The potential association between baseline and clinical characteristics and HIV testing and HIV RNA PCR testing was assessed using bivariate analysis (Fisher exact, χ^2, and Student *t* tests) and analysis of variance for continuous data

Table 2. CSF Testing and Analysis in 1292 Patients With Meningitis or Encephalitis by HIV Testing and Results

Variable	HIV Test Not Performed (n = 650)		HIV Test Performed (n = 642)		P*	HIV Test Negative (n = 566)		HIV Test Positive (n = 76)		P**
	No. (%) or Median (Range)		No. (%) or Median (Range)			No. (%) or Median (Range)		No. (%)		
Cerebrospinal fluid microbiology testing										
Bacterial culture ordered	622/650	(96)	622/642	(97)	.031	548/566	(97)	74/76	(97)	.657
CSF analysis										
CSF WBC, cells/mm^3	172	(0–52 000)	100	(0–60 000)	.207	111.5	(0–60 000)	43	(0–5200)	.090
CSF RBC, cells/mm^3	30	(0–1 540 000)	25	(0–3 800 000)	.523	32	(0–3 800 000)	8	(0–2750)	.530
CSF protein, mg/dL	79	(0–1230)	72.5	(0–4537)	.099	73.5	(0–4537)	66.5	(0–1321)	.924
CSF glucose, mg/dL	54	(0–366)	54	(0–482)	.482	55	(0–482)	50	(0–134)	.068
Cerebrospinal pleocytosis										
Lymphocytic pleocytosis	87/596	(15)	101/595	(17)	.261	78/520	(15)	23/75	(31)	.001

Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cells; WBC, white blood cells.

* *P* value for comparing results between patients with and without HIV test requested; ** *P* value for results between patients with positive and negative HIV tests.

analysis. We considered $P < .05$ statistically significant. Significant variables on bivariate analysis were entered into a multivariable logistic regression analysis, and bootstrapping was used to internally validate the logistic model. The goodness of fit of the logistic model was examined by the Hosmer-Lemeshow test. All statistical analyses were performed with SPSS, version 25, for MAC.

RESULTS

Cohort

From 2000 to 2015, 1478 patients with a diagnosis of meningitis or encephalitis were screened for eligibility. We excluded 180 patients (80 patients were <17 years old, and 100 patients had a prior HIV diagnosis). Of the 100 patients with a prior HIV diagnosis, 2 patients had aseptic meningitis, 82 patients had encephalitis, and 16 patients had community-acquired bacterial meningitis. The remaining 1292 patients were eligible: 639 were female (49.5%), and 679 were Caucasian (52.6%). Nearly half of them (619, 47.9%) had aseptic meningitis; 255 (19.7%) patients had encephalitis, 288 (22.3%) had health care–associated meningitis, and 130 (10.1%) had community-acquired bacterial meningitis. Only 642 (49.7%) patients had an HIV test performed while admitted to the hospital (Table 1). Of the 642 patients who were tested for HIV, 76 (11.8%) were positive.

Clinical Characteristics of Patients Tested for HIV

Of the 1292 patients who had a CNS infection, patients were less likely to have an HIV test if they were Caucasian (266 of 600, 44%; $P = .000$). There was no difference in HIV testing based on gender or timing of CNS infection (before or after December 31, 2006). For physical findings, patients were more likely have an HIV test if they presented with fever >38°C (254 of 564, 45%; $P = .007$), seizures (108 of 631, 17%; $P = .000$), or sinusitis (47 of 549, 9%; $P = .001$) (Table 1). As shown in Table 1 there was no difference in HIV testing for focal neurologic abnormalities, Glasgow Coma Scale (GCS) score <15, headache, nausea, nuchal rigidity, otitis, or photophobia. HIV testing varied depending on the type of CNS infection ($P = .000$): 46% (285 of 619) of aseptic meningitis patients, 68% (174 of 255) of encephalitis patients, 30% (85 of 288) of patients with health care–associated meningitis, and 75% (98 of 130) of patients with community-acquired meningitis. Only 8 patients with aseptic meningitis obtained an HIV RNA PCR to rule out acute HIV seroconversion syndrome; all 8 results were negative. Patients who had CSF bacterial cultures ordered (622 of 642, 97%; $P = .031$) were more likely to have an HIV test (Table 2). There was no difference between groups with regards to CSF white blood cell (WBC) count, CSF red blood cell (RBC) count, CSF protein, CSF glucose, or CSF lymphocytic pleocytosis. Out of 642 patients who underwent HIV testing, patients with lymphocytic pleocytosis were more likely to have a positive test ($P = .001$).

Table 3. Predictors for HIV Testing in 1292 Patients With Meningitis or Encephalitis by Logistic Regression Analysis

Predictors	Odds Ratio	*P*	95% CI
Race	2.265	.000	2.101–3.617
Fever >38°C	1.418	.049	1.317–1.734
Seizures	2.689	.002	1.328–3.426

Hosmer Lemeshow test $P = .994$; all variables were internally validated with bootstrapping ($P < .05$).

As shown in Table 3, a multivariable logistic regression analysis found race, seizures, and fever >38°C to be independent predictive factors of a patient receiving an HIV test. The Hosmer-Lemeshow goodness-of-fit test yielded a *P* value of .994 for the logistic regression, demonstrating that no strong evidence supports lack of fit of the model. These variables were internally validated by using bootstrapping ($P < .05$).

Clinical Characteristics of Patients a With Positive HIV Test

Of the 642 patients who had an HIV test, results were positive for 76 (12%). Patients were less likely to test positive if they were Caucasian (24 of 75, 32%; $P = .022$) and more likely if they were tested before 2007 (57 of 76, 75%; $P = .000$). HIV results were not found to be different between genders. Patients were less likely to have positive test results if their GCS score was <15 (11 of 76, 14%; $P = .001$) or if they had seizures (4 of 76, 5%; $P = .003$) but were more likely to have a positive result if they had photophobia (37 of 73, 51%; $P = .000$). No significant difference of HIV results was found between groups with and without fever, focal neurologic abnormalities, headache, nausea, nuchal rigidity, otitis, or sinusitis. Positive results were found to differ based upon the type of CNS infection ($P = .000$): 53 of the 285 (19%) tested aseptic meningitis patients were positive for HIV, 7 of the 174 (4%) tested encephalitis patients were positive, 0 of the 85 (0%) tested health care–associated meningitis patients were positive, and 16 of the 98 (16%) tested community-acquired meningitis patients were positive. CSF lymphocytic pleocytosis (23 of 75, 31%; $P = .001$) was found to correlate with a positive HIV test. Furthermore, there were no significant differences either in CSF WBC, CSF RBC, CSF protein, or CSF glucose between the groups.

DISCUSSION

To our knowledge, this is the largest study to date to address HIV testing in adults with meningitis or encephalitis. Previous studies have had smaller sample sizes, included patients with a known HIV diagnosis, described only patients with either meningitis or encephalitis, or evaluated patients in developing countries with higher rates of HIV when compared with the United States [13–17, 20, 21]. We analyzed data on HIV testing for meningitis and encephalitis over a 16-year period and evaluated for predictors for patients to receive an HIV test and for the results to be positive.

Overall, the characteristics of our participants, who were newly diagnosed with HIV, correlate with the general demographic for a new HIV diagnosis [1]. Non-Caucasians and those tested before 2007 were more likely to have a positive HIV test ($P = .022$ and .000), which supports the CDC statistics that HIV incidence has been steadily declining from 2010 to 2016 but is still highest among African Americans and Latinos [2]. This suggests that physicians are more likely to test racial groups that are at higher risk of HIV. Our study failed to find significant differences in HIV incidence between genders ($P = .644$), which contradicts the CDC incidence rate between genders. But this difference can potentially be explained by the location of our study. Houston and New Orleans have a significantly higher proportion of non-Caucasians when compared with the rest of the United States, which can be a confounding variable when grouping by gender [22]. HIV testing significantly differed depending on the type of CNS infection. Community-acquired bacterial meningitis had the highest testing percentage (75%), while health care–associated meningitis had the lowest (30%). We speculate that this difference could possibly be explained by the type of physicians taking care of these 2 different types of CNS infections or because the cause of the health care–associated meningitis is usually known (postcraniotomy, post–trauma, or associated with an infected CNS device). Our study also documented that only 8 (1.2%) patients with aseptic meningitis were tested for acute HIV seroconversion syndrome with a plasma HIV RNA PCR during their admission. This could contribute substantially to the underdiagnosis of this treatable syndrome.

Since 2006, the CDC recommends that all patients in a health care setting be screened for HIV and that high-risk individuals be screened annually [3]. However, our results show that HIV testing failed to significantly increase in our cohort after the CDC made their recommendation ($P = .068$), and only half (49.7%) of our cohort was tested for HIV. This result supports the findings in a recent study by Vigil et al., which found that only 54% of patients who presented with community-acquired meningitis had been tested for HIV [23]. In a large nationwide study of 26 249 of adults with meningitis or encephalitis, Hasbun et al. found that only 4.2% had a known HIV infection [24]. Unfortunately, this study did not exclude patients who were already diagnosed with HIV or describe how many patients were tested for HIV. Similarly, in a very small study, Hanson et al. found that 5% of patients who were admitted to the hospital for acute meningitis were not appropriately diagnosed with HIV infection [25]. Meningitis in people living with HIV carries a higher burden. Domingo et al. found that people living with HIV have a 19 times greater risk of developing spontaneous bacterial meningitis than uninfected people [21]. In addition, it carries a worse prognosis and higher risk of disseminated infection. The high percentage of newly diagnosed patients in our study suggests that we need to foster awareness

of the importance of HIV testing in adults with meningitis or encephalitis in order to appropriately diagnose and treat them.

Our study has several strengths. This is one of the largest studies to evaluate HIV testing and factors associated with positive HIV results in adults with 4 types of CNS infections. Also, our large patient population allowed for a strong multivariable analysis that was internally validated with bootstrapping. However, there were still several limitations to our study. Because of the retrospective nature of our study, some data were not found in the electronic medical records, which could limit the conclusions of the study. The increase in encephalitis, health care–associated meningitis, and community-acquired meningitis patients post-2006 could be due to more complete electronic medical records or more accurate ICD-9 coding. We were not able to access patients' outside medical records, so we were unable to determine if patients had been screened for HIV before admission, which would have satisfied the CDC recommendations on HIV testing. Another limitation is the fact that our patient population is from Houston and New Orleans, so the results of this study may not be generalizable to other cities in the United States, where the epidemiology of HIV may be different.

In conclusion, HIV testing remains an underutilized tool in the evaluation of adults presenting with CNS infections. Despite the HIV testing CDC recommendations, a large proportion of the patients in our study were not tested for HIV while being evaluated and treated for CNS infections. We need to foster awareness of the importance of HIV testing in all adults presenting with a CNS infection to improve not only an earlier diagnosis and therapy of HIV infection but also to help clinicians in formulating a differential diagnosis for the presenting CNS infection.

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