



Unsuspected HIV Infection in Patients Presenting with Acute Meningitis

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Abstract (Revised)

Background: Symptoms suggesting aseptic meningitis (fever, headache, meningismus) are relatively common during primary HIV infection (PHI), and other central nervous system (CNS) infections can complicate the course of chronic HIV disease. The proportion of patients presenting with meningitis who have undiagnosed HIV infection is not known. Determining the prevalence of HIV infection in this population may impact HIV testing recommendations.

Methods: Residual cerebrospinal fluid (CSF) specimens from patients aged 16-65 years who had herpes simplex virus (HSV) PCR testing requested between 1 Jan 1999 and 31 Dec 2004 were retrospectively tested for HIV RNA using the UltraSensitive COBAS Amplicor HIV-1 Monitor Test (Roche Diagnostics). Transplant recipients and those with known HIV infection were excluded. After medical and laboratory records were reviewed, all identifiers were removed from the database and specimens prior to testing. A CSF pooling strategy that combined 0.1 ml aliquots from 10 separate patients was used for sample analysis. When HIV RNA was detected in a pool, each of the 10 component samples were retested individually. The study was approved by the Duke IRB.

Results: 72 of 288 patient samples tested for HIV RNA (25%) had abnormal CSF indices (> 5 nucleated cells/mm³ and protein > 50 mg/dl). Among the 72 patients with inflammatory CSF, 57 (79%) had documented symptoms of meningitis/encephalitis. HIV RNA was detected in the CSF of 3/57 patients (5%) with clinical and laboratory findings indicative of CNS infection. Two of the 3 patients presented to the emergency department with a syndrome suggestive of PHI (fever, headache, malaise, and CSF lymphocytic pleocytosis with negative cultures and HSV PCR). Both had high levels of HIV RNA detected in CSF (157,000 and 106,000 copies/ml, respectively). The third patient was hospitalized with invasive pneumococcal disease and had a CSF HIV RNA of 124 copies/ml. HIV infection was not diagnosed prospectively in any of the three. Of the 57 patients with clinical and laboratory findings of meningitis/encephalitis, 33 (58%) had a HIV antibody test done during their evaluation but only 4 (7%) also had HIV PCR done.

Conclusions: Unsuspected HIV infection, including PHI, is relatively common among patients with acute meningitis. Patients with clinical and laboratory findings suggestive of meningoencephalitis should have HIV testing, including a nucleic acid test, performed as a part of the diagnostic evaluation.

Objectives

We sought to determine the prevalence of unsuspected HIV-1 infection in patients presenting to our institution with acute aseptic meningitis and/or encephalitis of uncertain etiology. The prevalence HIV infection in this population may have important diagnostic and management implications.

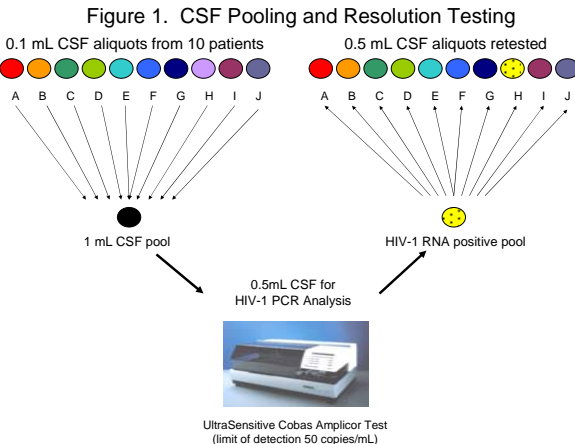
Materials & Methods

Specimens: The Duke Clinical Microbiology Laboratory catalogs and freezes all residual CSF at -80°C after the requested nucleic acid amplification tests have been performed. To identify patients with suspected aseptic meningitis, laboratory requests for HSV PCR testing on CSF between 1 January 1999 and 31 December 2004 were reviewed.

Patients: Residual CSF samples from patients between the ages of 16 and 65 years, who were not known to have HIV infection, were retrieved from the freezer. Transplant recipients were excluded from the study.

Clinical Data: Medical and laboratory records were reviewed to ascertain presenting signs and symptoms prompting lumbar puncture (LP). In addition, CSF profiles and microbiologic test results were recorded. Standard case definitions for meningitis and encephalitis were applied to each case.

HIV testing: All identifying personal health information was removed permanently from the study database and clinical samples prior to HIV RNA nucleic acid testing using the UltraSensitive COBAS Amplicor HIV-1 Monitor Test (Roche Diagnostics). A CSF pooling strategy that combined 0.1 mL aliquots from 10 separate patients was used for sample analysis (figure 1). If HIV RNA was detected in a pool, each of the anonymized individual specimens were retested separately. HIV testing without patient consent is explicitly permitted for the purposes of epidemiologic investigation to ascertain case rates in specific populations. The investigators were unable to link HIV test results to individual subjects in the database/specimen repository after testing.



Results

During the 6 year study period, 1659 CSF specimens from 1458 individual patients were submitted to the Duke Clinical Microbiology Laboratory for HSV PCR testing (figure 2). Thirty-four percent of patients (496/1458) met the study criteria and 58% (288/496) had residual frozen CSF available for testing. The study demographics are displayed in table 1. Twenty-five percent (72/288) of subjects had abnormal CSF indices (> 5 nucleated cells/mm³ and protein > 50 mg/dl) and 57 of the 72 with inflammatory CSF also had clinical signs of meningitis or encephalitis. HIV-1 RNA was detected in the CSF of 3 patients (table 2), all of whom were evaluated in the hospital with clinical and laboratory markers of CNS infection. HIV infection was not diagnosed prospectively in any patient. A significant minority of study subjects had their LP performed in the emergency department (ED) and were discharged to home with a diagnosis of aseptic meningitis. Thirty-four percent of subjects (98/288) had an HIV ELISA performed and only 5.2% (15/288) also had an HIV-1 plasma viral load done as a part of their clinical evaluation for meningitis.

Figure 2. Study Design

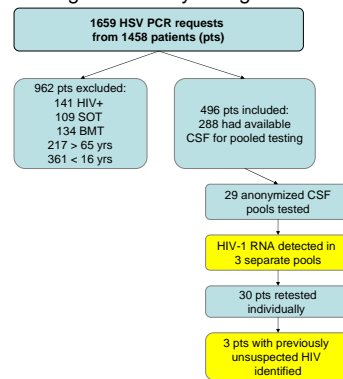


Table 1. Demographics

| N=288 | Age (median, range) | 40 years (16 – 65) |
|--------------------------------------|---------------------|--------------------|
| Sex | | |
| Male | 119 (41.3%) | |
| Female | 169 (58.7%) | |
| Ethnicity | | |
| Caucasian | 146 (50.7%) | |
| Black | 107 (37.2%) | |
| Hispanic | 22 (7.6%) | |
| LP location and disposition | | |
| ED/acute care (no. admitted from ED) | 112 (38.9%) | 51/112 (45.5%) |
| Hospital | 176 (61.1%) | |
| Clinical Diagnosis | | |
| Meningitis/Encephalitis | 57 (19.8%) | |
| CSF parameters | | |
| >5 cells/mm ³ only | 31 (10.8%) | |
| >50 mg/dL protein only | 70 (24.3%) | |
| both | 72 (25.0%) | |
| HIV testing | | |
| Ab only | 98 (34.0%) | |
| PCR | 15 (5.2%) | |

Table 2. HIV Positive Subjects

| Subject | Presentation | CSF HIV-1 RNA (copies/mL) |
|--------------|--|---------------------------|
| 39 y.o. male | Aseptic meningitis with a rash | 157,000 |
| | Discharged from the ED | |
| 28 y.o. male | Aseptic meningitis | 106,000 |
| | Discharged from the ED | |
| 37 y.o. male | Seizure and altered mental status | 124 |
| | Blood cultures grew <i>S. Pneumoniae</i> | |
| | Expired in the hospital | |

Discussion

The evaluation of patients with suspected CNS infection is often challenging. The term "aseptic" meningitis refers to a clinical and laboratory syndrome of meningeal inflammation with negative cultures. HIV is one of a number of viruses that can cause aseptic meningitis. Viral invasion of the CNS occurs early during PHI and approximately 24% of patients will develop aseptic meningitis (Kahn et al. NEJM 1998; 399: 33-39). CSF HIV-1 RNA levels have been shown to be significantly higher in patients with acute infection as compared to chronically infected controls (Picher et al. AIDS 2001; 15: 837-845). Identification of patients with PHI or chronic HIV infection allows for the interruption of transmission and initiation of treatment. Five percent of patients (3/57) in our study with clinical and laboratory features of aseptic meningitis were found to have HIV infection that had not been diagnosed prospectively. Two of the 3 subjects likely presented with PHI given their high CSF HIV-1 viral load and symptoms. Both were evaluated in and discharged from the ED.

Conclusions

- 1) Clinicians should have a high index of suspicion for HIV infection in patients at-risk of acquisition of the virus who present with aseptic meningitis of uncertain etiology.
- 2) Blood for HIV-1 RNA testing and an HIV ELISA should be obtained when an at-risk patient presents with aseptic meningitis or encephalitis.
- 3) Because many at-risk patients are evaluated only in the ED, HIV testing/counseling programs need to be adapted for urgent care settings.

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