Brain Biopsy in Patients With Acquired Immunodeficiency Syndrome

Diagnostic Value, Clinical Performance, and Survival Time

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Background: Despite extensive discussion in recent years, brain biopsy in patients positive for human immunodeficiency virus who manifest cerebral mass lesions remains an ill-defined step in management.

Methods: Prebiopsy data of 26 human immunodeficiency virus–positive patients with cerebral mass lesions who underwent computed tomography–guided stereotactic brain biopsy (SBB) were reviewed by a specialist in infectious diseases and by a neuroradiologist to establish a clinical diagnosis and a treatment plan for each patient. The postbiopsy diagnosis was compared with the prebiopsy diagnosis. Long-term patient outcome after SBB was recorded by means of a clinical performance scale to estimate its impact on life expectancy and clinical performance.

Results: The SBB was diagnostic in 25 patients (96%). Potentially treatable disease was diagnosed in 21 patients (81%), and specific therapy was initiated in 17 patients (65%); 10 patients (39%) were able to complete therapy. The SBB corroborated the clinical diagnosis in 13 (52%) of 25 patients. The group with identical clinical and biopsy-proved diagnoses showed significantly better response to therapy ($P = .02$), clinical performance ($P = .04$), and survival after biopsy ($P = .01$), as compared with the group with different clinical and biopsy-proved diagnosis, although no significant difference was found for the degree of immunosuppression. Only completion of the treatment plan increased life expectancy significantly ($P = .008$).

Conclusions: These data show that in human immunodeficiency virus–positive patients with brain mass lesions, SBB has a high diagnostic yield. A subgroup of patients will benefit from specific therapy guided by the SBB result. The procedure should, however, be strictly limited to patients able to tolerate specific therapy.
PATIENTS AND METHODS

PATIENTS

Twenty-six HIV-positive patients underwent SBB of a cerebral mass lesion in our institution between October 1, 1987, and May 31, 1996. Medical records, imaging studies, and follow-up data were reviewed for all patients. The median age at biopsy was 35 years (range, 24-61 years); 19 patients were men and 7 were women (male-female ratio, 2.7:1). Risk groups for HIV infection were as follows: intravenous drug abuse, 10 (38%); homosexual, 8 (31%); and heterosexual contact with HIV-positive partner, 8 (31%). The median time between the first positive HIV test and biopsy was 33.3 months (range, 0.2-119.5 months).

The median CD4+ cell count in the peripheral blood at the time of presentation was 36 × 10^6/L (range, 0.468 × 10^6-10^6/L). Clinical categories according to the Centers for Disease Control and Prevention classification system were as follows: A3, 2 patients (8%); B3, 7 (27%); and C3, 15 (58%). One patient had cerebral toxoplasmosis as the primary manifestation of HIV infection. The other patients reported previous disease manifestations before the current hospitalization. These disease manifestations were recorded according to the Swiss HIV Cohort Study. Among these, the most often reported manifestations were Candida stomatitis (19 patients [73%]), Pneumocystis carinii pneumonia (10 [38%]), weight loss (9 [33%]), Candida esophagitis (7 [27%]), and herpes zoster episodes (5 [19%]).

Computed tomography–guided stereotactic biopsy was performed taking multiple biopsy specimens (average, 3-2) along a single trajectory through the lesion and its margins (Brown-Roberts-Wells Stereotactic System and the Cosman-Roberts-Wells Stereotactic System, Radionics, Burlington, Mass).

INDICATIONS FOR SBB

The following indications were found: no response to empiric antitoxoplasmosis therapy for 10 to 14 days (13 patients [50%]), development of symptoms under primary antitoxoplasmosis prophylaxis (8 [31%]), secondary antitoxoplasmosis prophylaxis (2 [8%]), mass lesion not suggestive of toxoplasmosis origin (7 [27%]), and negative Toxoplasma serostatus (3 [12%]). Some patients had more than 1 indication for SBB.

PATHOLOGIC AND MICROBIOLOGICAL PROCESSING

In addition to direct examination, samples were sent for histopathologic and microbiological examination. All samples were fixed and prepared for histologic and immunocytochemical staining. Microbiological investigations were performed for viruses, aerobic and anaerobic bacteria, and mycobacteria as well as fungi. Techniques performed varied during the study period but represented the standard practice.

PRELIMINARY DIAGNOSIS

To establish the value of additional information from SBB, a specialist in infectious diseases (A.I.) and a neuroradiologist (P.M.) carefully reviewed all available prebiopsy clinical, laboratory, and imaging data in a blinded fashion and they defined a clinical (prebiopsy) diagnosis. The following information was known for all 26 patients: age, sex, risk group, duration of known HIV infection, CD4+ cell count, previous disease manifestations, development of current symptoms, previous and present therapy, laboratory results, and a prebiopsy contrast computed tomographic scan (in 9 patients magnetic resonance images and in 3 patients positron emission tomographic scans were available in addition). The prebiopsy diagnosis was then compared with the results of SBB.

DEFINITIONS

Toxoplasmosis, cerebral lymphoma, Kaposi sarcoma, metastasis, and viral encephalitis were regarded as potentially treatable lesions. No specific treatment was available for patients with PML during the study period.

A modified Karnofsky performance scale (Clinical Performance Scale [CPS]) was used to determine clinical performance retrospectively at least twice every month after biopsy. To facilitate evaluation of the CPS grade, 3 criteria were analyzed: description of the clinical state, the degree of disability in daily activity, and examples of disease manifestations corresponding to this grade (in parentheses). This scale is divided into 7 grades as follows: 6: excellent clinical state, minor disease manifestation, patient lives independently (oral candidiasis); 5: good clinical state, moderate disease manifestation, patient lives largely independently, symptoms do not interfere with daily activity (chronic cough); 4: fair clinical state, major disease manifestation, patient under close follow-up/temporary hospitalization, limited daily activity (moderate hemisindrome); 3: poor clinical state, major disability, patient hospitalized, normal consciousness level (hemiplegia); 2: very poor clinical state, patient severely disabled, permanently hospitalized or in nursing home, contact possible (patient not oriented, bedfast); 1: patient stuporous or comatose; and 0: dead. Response to treatment was recorded in accordance with the definitions shown in Table 1.

STATISTICAL ANALYSIS

The Mann-Whitney U test and the Wilcoxon matched-pairs signed rank test were used for the statistical evaluation of subgroups; the Spearman rank test was used for analysis of correlations.

Comitantly, extensive efforts were made to improve the diagnostic rate of biopsy with the introduction of routine immunohistochemical analysis, electron microscopy, polymerase chain reaction, and even animal testing.13-16 Progress has been made in the treatment of cerebral lymphoma.17-19 New diagnostic and therapeutic strategies were developed for the treatment of progressive multifocal leukoencephalopathy (PML).20-22 Even though the number of guidelines regarding patient management increased recently, little is known about the overall benefit of brain biopsy in HIV-positive patients.14,23-26 Several studies have reported the diagnostic rate of computed tomography—
guided stereotactic brain biopsy (SBB) as well as the number of potentially treatable conditions found, but none of the studies addresses the overall benefit of SBB regarding treatment, life expectancy, and quality of life.\textsuperscript{6,14}

Introduction of combination treatments for HIV infection, such as highly active antiretroviral therapy (HAART), has steadily decreased the number of patients with severe clinical disease manifestation in industrialized nations.\textsuperscript{29} However, since financial resources for medical care in the developing world are limited, and the emergence of multiple drug resistance was recently reported, this problem will probably remain of interest.\textsuperscript{30} Moreover, a certain proportion of patients have central nervous system lesions as the initial manifestation of their HIV infection. The purpose of this study was to analyze the diagnostic value and impact of SBB for cerebral mass lesion on treatment, long-term outcome, and survival of HIV-positive patients.

RESULTS

BIOPSY RESULTS

Stereotactic biopsy disclosed a definite diagnosis in 25 (96%) of 26 patients: high-grade B-cell lymphoma was found in 11 patients (42%); cerebral toxoplasmosis in 6 patients (23%); PML in 4 patients (15%); viral encephalitis in 2 patients (8%); and metastasis and Kaposi sarcoma in 1 patient each (4%). In both cases of viral encephalitis, the histological examination stated “changes comparable with an acute viral encephalitis,” but immunostaining and polymerase chain reaction did not result in a more specific diagnosis.

Biopsy was nondiagnostic in 1 patient (4%); this patient’s condition responded well to atovaquone and clindamycin hydrophosphate for toxoplasmosis prescribed on the basis of clinical data despite unsuccessful previous antitoxoplasmosis therapy. There were 2 major postoperative complications (8%); both were intracerebral hemorrhages. One patient had cerebral lymphoma and died 2 days after biopsy. The other patient had PML and showed deterioration of his hemiparesis; he died 3 months later.

MANAGEMENT AND RESPONSE TO TREATMENT

Four patients had PML, and no specific treatment could be offered at the time of the study. In 1 patient, SBB was not diagnostic. In 21 patients (81%) a potentially treatable condition was diagnosed with SBB; 17 (65%) started specific therapy and 10 (38%) were able to complete specific therapy. Clinical deterioration (3 patients), death (2 patients), multiple drug allergy (1 patient), and depression (1 patient) led to interruption of treatment before completion in 7 patients (41% of all patients who started specific therapy). In 4 (19%) of 21 patients with a potentially treatable disease (all cerebral lymphoma), no specific therapy was initiated because of a marked deterioration after biopsy or a poor clinical state (CPS grade 4 and lower) at the time of the biopsy result. The condition of 1 of these 4 patients deteriorated after a major complication of SBB.

Of 17 patients who started specific therapy based on the biopsy result, 6 showed an excellent or good response, 6 had a poor or transient response, and 5 did not respond to therapy. The overall response rate (excellent or good response), excluding the patient with a nondiagnostic biopsy, was therefore 23% (Figure 1).

Five patients with toxoplasmosis completed therapy; 2 showed an excellent, 2 a good, and 1 a poor response. One patient died shortly after biopsy despite initiation of treatment. Four patients with cerebral lymphoma underwent a complete course of radiotherapy; of these, 1 each was in the excellent, good, transient, and no-response groups. Three patients with lymphoma did not complete radiotherapy; 1 showed a poor, 1 a transient, and 1 no response. Four patients with cerebral lymphoma did not undergo irradiation because of a marked recent decrease in clinical performance (of these, 1 pa-
After SBB-induced cerebral hemorrhage. Two patients with viral encephalitis received medical treatment (acyclovir and ganciclovir). In both, the histological diagnosis of acute viral encephalitis could not be further specified by immunostaining or polymerase chain reaction. One patient showed a transient good response to acyclovir; he died 52 days later, and autopsy disclosed cytomegalovirus ventriculitis. The other patient did not respond to antiviral drug therapy and died 3 days later. Radiotherapy was started in the patient with Kaposi sarcoma, but only a transient response was observed. The patient died 51 days later; the autopsy report described multiple Toxoplasma abscesses but did not mention histological alterations seen in cases with Kaposi sarcoma. No response to radiotherapy was seen in a patient with metastasis of a lung cancer.

SURVIVAL AFTER BIOPSY

Median survival (mean ± SD; range) after biopsy was 61 days (222 ± 394.3; 2-1584) and was inversely correlated with the time interval between first HIV-positive test and SBB (P = .02). No significant correlation was found for age, risk group, CD4+ T cells, number of previous disease manifestations, or CPS grade at the time of biopsy. Median survival in patients with cerebral Toxoplasmosis infection was found to be 147 days (517.8 ± 654.9; 3-1584); in patients with cerebral lymphoma, 61 days (136.9 ± 175.8; 2-580); and in patients with PML, 24 days (136.9 ± 175.8; 2-580). Median survival of patients without specific therapy was 24 days (50.7 ± 49.0; 2-137), whereas patients receiving an incomplete therapy course lived for 36 days (50.3 ± 56.4; 3-171). Completion of treatment increased life expectancy significantly to a median of 161 days (400.2 ± 501.2; 52-1584; P = .008).

COMPARISON OF PRELIMINARY AND BIOPSY DIAGNOSES

Thirteen (52%) of 25 clinical (prebiopsy) diagnoses established by the specialist of infectious diseases and the neuroradiologist on the basis of clinical and imaging data were confirmed by SBB. Twelve clinical diagnoses (48%) differed from the biopsy result and would have resulted in a different therapy in 8 patients (31%). In 4 patients (15%), biopsy diagnosis was PML and therefore did not result in specific therapy. A detailed analysis of concordant or different diagnosis based on clinical vs biopsy data is given in Table 2.

Comparison between the group with correct clinical diagnosis vs patients with a different biopsy diagnosis showed a significantly better response to specific therapy (P = .02), clinical performance (P = .04), and survival after biopsy (P = .01) in the group with concordant diagnosis. No significant difference was found for age, risk group, CD4+ T cells, number of previous disease manifestations, or CPS grade at time of biopsy. However, patients with a discordant diagnosis showed a tendency to more previous disease manifestations. All patients with excellent or good response to therapy (n = 6) were found in the group correctly diagnosed on the basis of prebiopsy data. In contrast, clinical improvement was found in only 3 (25%) of 12 patients with differing diagnosis (poor and transient response only). Median survival (mean ± SD; range) after biopsy was 137 days (267.2 ± 414.1; 10-1584) in patients with discordant diagnosis vs 52 days (61.1 ± 51.3; 2-171) in patients with differing diagnoses (P = .01) (Table 3).

AUTOPSY RESULTS

Autopsy was performed in only 6 patients (23%) 51 days (median) after the biopsy procedure. It confirmed the SBB result in 4 patients (3 patients with lymphoma and 1 with PML) but disclosed additional cerebral abnormalities in 2 of those patients with lymphoma. Autopsy reports showed cytomegalovirus encephalitis in 1 patient (19 days after biopsy) and cytomegalovirus ventriculitis in another (52 days after biopsy) in addition to lymphoma. An autopsy diagnosis that differed from the SBB diagnosis was seen in 2 cases. In 1 patient, the SBB diagnosis was cerebral Kaposi sarcoma, but autopsy disclosed multiple Toxoplasma abscesses. This

Table 2. Comparison Between Clinical (Prebiopsy) Diagnosis and Result of Stereotactic Biopsy

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Lymphoma</th>
<th>Toxoplasmosis</th>
<th>PML</th>
<th>Encephalitis</th>
<th>Metastasis</th>
<th>Kaposi Sarcoma</th>
<th>Total</th>
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<td>11</td>
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<td>0</td>
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<td>6</td>
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<tr>
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<td>4§</td>
<td>0</td>
<td>0</td>
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<td>4</td>
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<tr>
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<td>0</td>
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<td>2</td>
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<tr>
<td>Metastasis</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nondiagnostic</td>
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<td>0</td>
<td>0</td>
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<td>1</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>26</td>
</tr>
</tbody>
</table>

*PML indicates progressive multifocal leukoencephalopathy.
†In 2 of these patients, autopsy was performed and confirmed the diagnosis in 1 patient (36 days after biopsy) but demonstrated multiple Toxoplasma abscesses, human immunodeficiency virus encephalitis, cytomegalovirus, and probable Cryptococcus meningitis in the other patient (5 months after biopsy).
‡Autopsy performed 19 days after biopsy showed cerebral lymphoma and cytomegalovirus encephalitis.
§Autopsy in 1 of these patients confirmed PML (2 days after biopsy).
¶Autopsy in 1 of these patients showed cerebral lymphoma (as suggested clinically) in addition to cytomegalovirus ventriculitis (52 days after biopsy).
¶¶Autopsy 51 days after biopsy disclosed cerebral toxoplasmosis.
Involvement of the central nervous system is one of the prominent findings in patients with acquired immunodeficiency syndrome, and rapid and precise diagnosis is essential for optimal patient management. Although important progress was seen in imaging and molecular biology techniques during the last decade, cerebral stereotactic biopsy is the only reliable method of obtaining histological diagnosis.

Stereotactic brain biopsy is highly sensitive (96%) in diagnosing cerebral mass lesions in HIV-positive patients, but it carries a significant risk of major complications (8%), emphasizing the importance of defining indications for this invasive procedure in this group of patients.33 No specific therapy was given in 31% of all patients after diagnosis for 1 of 2 reasons. First, the patient's clinical state may have been so poor or markedly decreasing at the time of definite diagnosis that initiation of specific therapy seemed unreasonable. Second, no proved specific treatment could be offered to patients with PML at the time of the study. However, a recent study showed significant benefit of highly active antiretroviral therapy (HAART) in patients with HIV-associated PML. Therapy and prognosis therefore may change in the near future.21,22,34

Specific therapy was started in two thirds of patients; nearly half of them, however, did not complete treatment. Interestingly, patients who completed the therapy protocol showed a significantly longer survival time and a significant increase in clinical performance. Incomplete treatment did not increase life expectancy, even though a transient response to therapy was seen in most patients. The large number of patients who received no treatment or an incomplete course of therapy (58%) after SBB emphasizes that indication for cerebral biopsy should be strictly limited to patients able to support a specific and complete course of therapy.33 According to the CPS used in this study, this corresponds to grade 3 or greater. Figure 2 shows a decision analysis that summarizes the conclusions of our study for the management of HIV-positive patients with cerebral mass lesions.

Survival and clinical performance after stereotactic biopsy correlated well with the clinical response to specific therapy, but no correlation was found between survival time and other factors such as age, sex, risk group, CD4+ count, time since first positive HIV testing, or CPS grade at the time of biopsy. This seems to indicate the critical role of cerebral disease on life expectancy in patients with acquired immunodeficiency syndrome.

Since brain biopsy is the only method for tissue diagnosis of cerebral mass lesions, case-control pairs could not be obtained. Medical records from the treating physicians in most cases did not reflect a definite prebiopsy diagnosis. To overcome this, all prebiopsy data were reviewed in a blinded fashion as to SBB result by a specialist in infectious diseases and a neuroradiologist to establish diagnosis and treatment plan for each individual patient. The comparison of prebiopsy and postbiopsy diagnosis and treatment plan, as well as autopsy report, if available, and scoring of long-term outcome allowed us to extrapolate the value of SBB in this group of patients.

Clinical diagnosis based on prebiopsy data showed a correct diagnosis compared with the biopsy result in...
about half of all patients. Similar results were found in a recent study by Everall et al\textsuperscript{34} comparing magnetic resonance imaging and neuropathology data in patients with acquired immunodeficiency syndrome.\textsuperscript{35} No significant difference between groups of patients with concordant vs discordant biopsy and clinical diagnosis was found for age, sex, time after first HIV-positive testing, and CD4\textsuperscript{+} count. Interestingly, most patients who showed clinical amelioration after specific therapy and all patients with good or excellent responses were found in the group of patients with identical clinical and biopsy diagnoses. This might be at least partly explained by the kind of cerebral disease found, since these patients more often showed cerebral lymphoma or toxoplasmosis, both with good treatment options and life expectancy. In contrast, patients with a different clinical and biopsy diagnosis showed a broader spectrum of cerebral diseases (5 vs 3) and a higher proportion of patients with PML, a disease associated with a poor prognosis. Moreover, these patients showed a tendency to higher numbers of HIV-associated disease manifestations before biopsy. Likewise, initiation of specific therapy, response to therapy, and life expectancy were significantly decreased in this group.

Why is it that a more complex clinical and imaging appearance is associated with a worse response to therapy for a histologically confirmed diagnosis? One explanation may be residual manifestation of a previous disease, or the coexistence of other cerebral pathologic processes, in addition to the one diagnosed by biopsy. Multiple coexisting cerebral diseases may account for the less characteristic clinical and imaging features as well as for the low response rate to therapy, a worse clinical outcome, and decreased survival time despite specific therapy in this group of patients. Heterogeneous underlying cerebral disease was found in more than half of cases examined by magnetic resonance imaging and neuropathologic studies, especially in brains with diffuse white matter lesions.\textsuperscript{36} Multiple coexisting cerebral diseases in more than a third of all patients who died of HIV-associated neurologic disorders were reported in a large neuropathologic study.\textsuperscript{2} The same study reported a high percentage of pathologic cerebral alterations in neurologically intact HIV-positive patients.

Autopsy was performed in only 6 patients in the present series, and multiple coexisting cerebral diseases were found in half of them. Autopsy added more cerebral pathologic processes to the biopsy diagnosis in 2 patients and invalidated the SBB diagnosis in another 2 patients (false positive). This might be explained by therapeutic cure of the disease subjected to biopsy and subsequent development of a new pathologic process, 2 or more coexisting diseases, or erroneous histopathologic interpretation. Indeed, one of these patients was given radiotherapy for biopsy-“proved” Kaposi sarcoma; he showed a transient clinical response but died 51 days later. The other patient did not receive specific treatment. However, this throws light on 2 important issues that may limit the value of SBB. First, what is the rate of false-positive results after SBB in HIV-positive patients? Even though examination of the tissue obtained may show a pathologic process, it might not necessarily represent the leading cause of the neurologic deficit. Second, can SBB identify multiple coexisting cerebral pathologic processes? To answer these questions, further studies are necessary to compare biopsy and autopsy diagnosis.

In conclusion, this study favors the view that selected HIV-positive patients with cerebral mass lesions harbor a high proportion of treatable lesions and can benefit from information added by SBB. In more than half of patients in the subgroup who show clinical and imaging features in accord with the SBB result, specific therapy achieved excellent or good clinical responses. Excellent or good clinical response was found in less than half of the patients treated. However, contradicting clinical and imaging features represent a poor prognostic factor despite the introduction of specific treatment. It is, however, safe to say that this is an estimate of the worst scenario, as the proportion of patients responding to therapy should increase with the advent of new and more efficient treatment protocols, as well as with stricter patient selection for SBB.

Accepted for publication March 2, 1999.

Presented in part as a poster at the annual meeting of the American Association of Neurological Surgeons, Denver, Colo, April 12-17, 1997.

Nicolas de Tribolet, MD, Department of Neurological Surgery, University Hospitals in Lausanne and Geneva, Switzerland, provided continuous support and encouragement.

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