



SHORT REPORT

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# Brain biopsy in AIDS patients: diagnostic yield and treatment applications

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## Abstract

**Objective:** Central nervous system involvement in AIDS patients can present at any stage of the disease. Brain lesions detected in imaging studies are usually treated empirically. A brain biopsy is indicated in the absence of clinical and radiologic improvement. In the present study, 16 AIDS patients underwent brain biopsy. We evaluated the diagnostic yield of the brain biopsy and the changes in the disease course.

**Materials and methods:** Sixteen consecutive AIDS patients (12 men, 4 women; mean age 40.8 years) underwent a brain biopsy at Sheba Medical Center between 1997 and 2009. A retrospective analysis was performed and the clinical outcome was recorded.

**Results:** Median CD4 count before biopsy was 62.6. Magnetic resonance images revealed multiple lesions in 12 patients and enhancing lesions in 12 patients. A total of 19 biopsies were performed in 16 patients. In the present series, the initial procedures provided a diagnostic yield of 81.25% (13 diagnostic cases from 16 procedures in 16 patients). Two of these patients underwent repeated biopsies that were eventually diagnostic. If repeated biopsies were taken into consideration, the diagnostic yield was 93.75% (15 diagnostic cases in 16 patients). The rate of hemorrhagic complications was 10.5% (2 hemorrhages in 19 procedures).

Pathologic examination revealed parasitic and fungal infections in 6 patients (6/16; 38%), progressive multifocal leukoencephalopathy in 4 patients (4/16; 25%), AIDS encephalopathy in 4 patients (4/16; 25%), and lymphoma in 1 patient (1/16; 6%). One patient had a nonspecific inflammatory process (6%). The treatment modality was modified in 12 patients and led to clinical and radiologic improvement in 8 patients.

**Conclusions:** Brain biopsy should be considered when empiric treatment of central nervous system lesions in AIDS patients fails. Biopsy is diagnostic in the majority of patients. The diagnosis allows for treatment modifications, which lead to clinical and radiologic improvement in some patients.

**Keywords:** HIV, Brain biopsy, CNS AIDS, Neuroimmunology

## Introduction

Central nervous system (CNS) involvement in AIDS patients is a well-established phenomenon that occurs in approximately 40% to 60% of patients at some stage of the disease. In 10% to 20% of patients, neurologic complications are the first manifestation of HIV infection [1]. The causes of brain involvement include infection, inflammatory changes, and neoplasia [2]. The most common brain lesion in HIV patients worldwide is toxoplasmosis [3], but there is an increased incidence of HIV-associated

tuberculosis in focal brain lesions in developing countries [4]. Imaging characteristics of brain lesions in HIV patients have been described [5,6]. The diagnostic yield of brain biopsy in HIV patients has also been evaluated [7-9]. In recent years, due to the availability of advanced multidrug therapies such as highly active antiretroviral therapy (HAART), the disease has gained more chronic characteristics and patient prognosis has greatly improved. The increased longevity of the clinical course of AIDS patients requires the establishment of more aggressive therapeutic approaches in patients with CNS involvement. Brain lesions detected on imaging studies are treated empirically according to current clinical guidelines.

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Brain biopsy is indicated in the absence of clinical and radiologic improvement, based on the recommendations of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America. The objective of this retrospective study was to analyze the data of 16 AIDS patients who underwent a brain biopsy at Sheba Medical Center in Israel to evaluate the diagnostic yield and changes in the disease course.

## Material and methods

### Patient selection and study approval

The study was conducted according to procedures approved by the Sheba Medical Center Institutional Review Board.

### Clinical data

Sixteen consecutive AIDS patients underwent a brain biopsy at Sheba Medical Center between 1997 and 2009. Patient characteristics; presenting symptoms; neurologic status; CD4 count; radiologic imaging results, including number of lesions, location of the targeted lesion, and presence of post-operative hemorrhage on computed tomography (CT) scans; and pathologic results were retrospectively analyzed. Treatment changes, and clinical and radiologic outcome were recorded.

### Surgical procedure

Stereotactic brain biopsies were performed using a Radiomics® CRW™ frame and localizer (except for one patient that underwent an open image-guided navigation system biopsy using pituitary forceps). After performing the CT scan and establishing the target (based on fusion with preoperative MR images and performed by the neurosurgeon), the patient was taken to the operating room and serial stereotactic biopsies were obtained under local anesthesia along the established trajectory using a side-cutting biopsy needle. CT scans were obtained up to 2 hours post-procedure and the patients remained in the neurosurgical department for overnight observation.

### Tissue analysis

Tissue specimens collected in the operation room were placed in individual vials for pathologic analysis; incubated in aerobic, anaerobic, mycobacterium, and fungal cultures; and subjected to PCR analysis for the JC and BK polyomaviruses.

## Results

Twelve patients were men. Mean age at onset of the neurologic manifestations was 40.8 years. The clinical manifestations of the disease were mainly cognitive changes and motor deficits. Mean CD4 count before the brain biopsy was 62.6. A total of 19 brain biopsies were

performed in 16 patients. In the present series, the initial procedures provided a diagnostic yield of 81.25% (13 diagnostic cases from 16 procedures in 16 patients). Two of these patients underwent repeated biopsies that were eventually diagnostic. If repeated biopsies were taken into consideration, the diagnostic yield was 93.75% (15 diagnostic cases in 16 patients).

Among the three patients with an initially nondiagnostic biopsy, the initial biopsy revealed a nonspecific inflammatory process in two patients, and the procedure was aborted due to hemorrhage in one patient. Two of these patients underwent a repeated biopsy that was eventually diagnostic.

One of the patients initially diagnosed with a nonspecific inflammatory process underwent two more biopsies and the third biopsy was eventually diagnostic. The second patient initially diagnosed with a nonspecific inflammatory process improved with HAART and did not require a second biopsy.

In the present series, the rate of hemorrhagic complications was 10.5% (2 hemorrhages in 19 procedures). Two of our patients had a hemorrhage; the first had a non-surgical bleeding however we had to abort the procedure and the patient underwent later a second procedure with a diagnostic biopsy. The second patient had a diagnostic biopsy, but due to clinical deterioration underwent evacuation of a hematoma. This patient recovered from the procedure, but did not improve with HAART.

Pathologic examination revealed parasitic and fungal infections in 6 patients (6/16) [38%]: toxoplasmosis, N = 4 [67%], aspergillosis N = 1 [17%], and cryptococcosis N = 1 [17%], progressive multifocal leukoencephalopathy (PML) in 4 (25%) patients, AIDS encephalopathy in 4 patients (25%), and lymphoma in 1 (6%) patient. One patient had a nonspecific inflammatory process (6%). The treatment modality was modified in 12 patients and led to clinical and radiologic improvement in 8 patients (Table 1).

## Discussion

Treatment with highly active antiviral drugs (HAART) has resulted in an overall decline in morbidity and mortality among HIV-infected patients with advanced disease [10]. The widespread use of prophylactic regimens has changed the disease pattern and decreased the incidence of opportunistic infections [11]. Vago et al. [12] reported on a large autopsy series that showed a significant reduction in the frequency of HIV-related central nervous system lesions in AIDS patients since the beginning of the HAART era.

In patients with HIV, *Toxoplasma gondii* is the most frequent infectious cause of focal brain lesions [3]. Toxoplasmic encephalitis has a subacute onset with focal

**Table 1 Patients demographic and clinical data**

Diagnosis	Age	SBX VS open	Sex	Solitary vs multiple	Target location	Side	Enhancement	Edema	Presenting symptoms	CD4 pre biopsy	Treatment	Complications	Clinical improvement
1 PML	37	sbx	Male	Multiple	BG	Right	No	None	Combined	69	AZT, 3TC	No	No
2 Non diagnostic × 1, Toxoplasmosis 2nd	36	sbx	Male	Solitary	Frontal	Right	Yes	Yes	Motor	50	AZT, 3TC, Antitoxoplasmosis	Bleeding	No
3 PML	41	sbx	Male	Solitary	BG	Left	No	None	Cognitive	10	AZT, 3TC	No	No
4 Lymphoma	39	sbx	Male	Solitary	BG	Right	Yes	yes	Motor	13	Radiation Therapy	No	Yes
5 PML	32	sbx	Male	Multiple	Frontal	Right	No	None	Combined	57	HAART	No	Yes
6 Toxoplasmosis	24	sbx	Male	Multiple	BG	Left	Yes	Yes	Combined	38	HAART, Antitoxoplasmosis	No	No
7 Toxoplasmosis	29	sbx	Male	Solitary	Frontal	Right	Yes	Yes	Motor	185	HAART, Antitoxoplasmosis	No	Yes
8 Non Diagnostic × 2 Aspergilosis 3rd	78	sbx	Male	Multiple	Parietal occipital frontal	Right	Yes	Yes	Motor	50	HAART, Amphotericin	No	No
9 HIV encephalopathy	33	sbx	Male	Multiple	Occipital	Right	Yes	Yes	Combined	3	HAART	No	Yes
10 PML	48	sbx	Male	Multiple	Frontal	Right	Yes	None	Combined	25	HAART	No	Yes
11 Non diagnostic inflamatory reactive process	41	sbx	Female	Multiple	BG	Left	Yes	Yes	Motor	22	HAART	No	Yes
12 Viral infection	37	sbx	Male	Multiple	Frontal	Left	Yes	Yes	Combined	36	HAART	No	No
13 Cryptococcal	55	sbx	male	Multiple	Temporal	Left	Yes	Yes	Motor	60	HAART, Amphotericin, Intraconazol	No	No
14 Viral infection	46	sbx	Female	Multiple	Occipital	Right	No	None	Combined	338	HAART	No	Yes
15 Viral infection	46	sbx	Female	Multiple	BG	Right	Yes	Yes	Combined	33	HAART	Bleeding	No
16 Toxoplasmosis	32	open	Female	Multiple	Parietal	Right	Yes	Yes	Combined	14	HAART, Antitoxoplasmosis	No	Yes

neurologic abnormalities frequently accompanied by headache, altered mental status, and fever [13].

Diffuse toxoplasmosis encephalitis should be considered in patients with anti-*T gondii* immunoglobulin G (IgG) antibodies and CD4 T-cell counts of <100/ $\mu$ L who present with unexplained neurologic disease.

Since the introduction of HAART, the incidence of toxoplasmic encephalitis has remained stable or decreased, CNS lymphoma has dramatically declined, PML has slightly increased, [11] and the incidence of HIV encephalopathy has increased [14]. Although combination therapies have decreased overall mortality and the prevalence of CNS opportunistic infections, these therapies may be less effective for preventing the direct effects of HIV-1 on the brain. One of our patients presented with histologic features of AIDS encephalopathy. The majority of patients in our cohort were men with a median age of 40, consistent with other studies [15,16]. These findings are compatible with our data, which is reported to be increasing in prevalence in the HAART era [17].

Thallium SPECT and PET scanning in the diagnosis of lymphoma and PCR analysis of the cerebrospinal fluid for the diagnosis of toxoplasmosis and JC virus have led to a shift in the use invasive diagnostic techniques (brain biopsy) to noninvasive diagnostic methods [5]. The patient in our series that was diagnosed with lymphoma had a solitary enhancing lesion. Although CNS lymphoma generally tends to enhance, atypical characteristics may be observed on MR images of immunocompromised patients [18]. Toxoplasma and lymphoma may have similar appearance on MR imaging. Erdag et al. [18] noted that lymphoma usually appears as a solitary lesion, unlike toxoplasmosis, which appears as a multifocal lesion. Only half of our patients with toxoplasmosis, however, had multifocal disease, similar to a previous report [15].

The majority of patients in our cohort that were diagnosed with PML had nonenhancing lesions, consistent with previous studies [18,19]. Other studies, however, report enhancement on MR images of PML patients that may reach 42% [15], and the development of a mass effect and temporary enhancement on MR images in the early phase of treatment might represent positive predictive factors for prolonged survival [19].

A literature review revealed several descriptions of stereotactic brain biopsy in AIDS patients. The majority of these were reports on patients treated in the pre-HAART era [7-9,16,20-26]. In a recent study, Rosenow et al. [15] divided a large cohort of 246 patients that underwent brain biopsy into two diagnostic groups, before and after the HAART era. The authors concluded that the introduction of HAART led to a steep decrease in the number of biopsies performed annually. Biopsy led to an objective and definitive diagnosis in 96% of patients (48/50), in the patients in the HAART era. Definitive diagnoses were

obtained for 91.3% of patients (179/196) in the pre-HAART era. The overall diagnostic yield of biopsy was 92.3% of the total patient cohort. Rosenow et al. [15] suggested that AIDS patients with intra-cerebral lesions should undergo toxoplasmosis titers, and those with negative toxoplasmosis titers should undergo early brain biopsy. In our study, the majority of the patients were treated in the HAART era, which may correlate with the relatively small cohort of patients that underwent stereotactic brain biopsy. The diagnostic yield of the biopsy was high, although lower than previously reported [15].

A total of 19 biopsies were performed in 16 patients; one procedure was aborted due to bleeding and three biopsies were nondiagnostic (15%). Significantly, two patients underwent repeated biopsies that were conclusive. Diagnoses were eventually obtained for 93.7% of patients (15/16). Based on the biopsy findings, the treatment modality was modified in 12 patients and led to clinical and radiologic improvement in 8 patients. Modification of the treatment following brain biopsy has also been reported [1,8].

Hemorrhagic complications of biopsy are reported [16,20,23,25]. The incidence of hemorrhage in our small cohort of patients was higher than that reported in a non-HIV group of patients treated in our department [27]. Although the coagulation profile in our patients was within normal limits, there may have been undetectable coagulopathy in this group of patients. Anticoagulation regimens have been suggested by others [16] and pre-biopsy correction of thrombopenia less than 100,000/ml is suggested by Rosenow et al. [15]. A larger cohort of patients is required to establish more definitive conclusions.

## Conclusion

We present the results from a single institute HAART era brain biopsy study in a cohort of 16 patients with active AIDS-associated lesions. Our objective diagnostic rates are consistent with those previously reported, allowing for treatment modification and confirming the usefulness of biopsy in these patients.

## Competing interest

The authors declare that they have no competing interests.

## Authors' contributions

ZZ and ZRC conducted the study, interpreted the data, and edited the manuscript. IL and VL were the primary care physicians of the patients, analyzed and interpreted the data. ZZ, ZRC, MH, and RS performed the surgical procedures or were part of the decision-making process. DN reviewed all the pathology and wrote the reports. CH reviewed all the radiological images. JB treated the oncology patient and interpreted the data. CG reviewed and interpreted the data and edited the manuscript. All authors read and approved the final manuscript.

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