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Research Article

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Brain Lesions: To Biopsy or Not to Biopsy: A Single Institution Retrospective Cohort

Aisenberg GM[1*], Lincoln JA[2], Lincoln CM,[3], Fenoy AJ[4] and Benjamin-Garner RA[5]

Abstract

Objectives: Patients presenting with intracranial lesions represent a diagnostic dilemma. Imaging and laboratory tests lack the specificity needed for decision-making. We aimed to detect what intervention and findings made the study patients eligible for brain biopsy, for observation or for treatment.

Methods: From January 2010 to December 2012, electronic medical records of 312 adult patients were selected from the hospital database using key words aimed to identify brain lesions, in two-affiliated tertiary-care, county-based hospitals in Houston, Texas. Decision to biopsy, to observe or to treat brain lesions was the main outcome variable. Clinical, laboratory and imaging information were correlated with the main variable to determine which factors made the need for biopsy more likely.

Results: Forty biopsied patients and 272 non-biopsied patients were included. Motor deficit, confusion or coma, single brain lesion, larger than 3 cm, with midline shift and complete ring enhancement made brain biopsy more likely, whereas bilateral brain or cerebellar lesion, presence of subcortical lesions with homogeneous enhancement, and history of cancer with potential for brain metastases made the biopsy less likely. Laboratory tests evaluated were inadequate surrogates of brain histology, whereas abnormalities on chest X ray or CT of the chest, abdomen or pelvis made the probability of brain biopsy lower. The above predictors for biopsy were not present among our HIV positive patients.

Conclusions: The path from lesion finding to the decision to observe, to treat or to biopsy was heterogeneous. Prospective validation and generalization to other institutions are needed to strengthen our observations.

Keywords:

Brain mass; Brain lesion; Brain infection; Brain abscess; Brain metastasis; Brain tumor; Stereotactic biopsy

Introduction

Patients with intracranial lesions represent a diagnostic dilemma. Computerized tomography (CT) or magnetic resonance imaging (MRI)can aid in the diagnosis by evaluating lesion properties such as extension, heterogeneity and gadolinium uptake [1,2]. Yet, these techniques lack enough diagnostic specificity [3,4]. Once the diagnosis of certain brain lesions is known or presumed, the available literature offers management recommendations, from which observation, empirical therapy, or surgery can be indicated [5-9]. On the contrary, we couldn't find a general approach to the problem we present here: the patient with a brain lesion without a known underlying diagnosis.

Modern biopsy techniques, especially stereotactic biopsy make possible to reach histological diagnosis with infrequent adverse outcomes [10,11].

In this retrospective study we describe the path that led from the discovery of brain lesions to the decision to observe, to treat or to biopsy, including the clinical, laboratory or imaging-based findings that made the patients eligible for any of those decisions.

Methods

The study was undertaken at Lyndon B. Johnson Hospital (LBJH) and Ben Taub General Hospital (BTGH), two affiliated tertiary-care, county-based centers in Houston, Texas, after obtaining Institutional Review Board approval (HSC-MS-12-0420); patient consent requirements were waived. We collected information from electronic medical records from January 1st2010 to December 31st2012.

Inclusion criteria

From the electronic common database for both hospitals we selected patients using the following identifiers: "brain lesion", "brain mass", "brain tumor", "brain metastasis", and "brain abscess". From that list, we distributed the patients in two groups: the first group consisted of those with a cerebral or cerebellar biopsy with diagnostic intention (**diagnostic biopsy group or DBP**). The second group consisted of patients that were not biopsied (**non biopsied group or NBP**). All patients were older than 18 years of age.

Exclusion criteria

We excluded patients if their final diagnoses, regardless of whether there was a biopsy performed, was attributed to trauma or cerebrovascular accident; if the biopsy, or resulting therapeutic intervention preceded the study period; if the brain tissue was obtained during a therapeutic craniotomy; or if the patients' poor clinical status prevented doctors from investigating their brain lesions.

We gathered the following indicators:

Demographic: Age, gender, ethnicity

Clinical: Signs and symptoms reported in the medical records such as headache, motor or sensory deficit, confusion or coma, vomiting, hypertension, memory loss, seizures, tremor.

Management: Admission requirement and length of stay, time from admission to intervention and from finding date to the date when an intervention (including observation) was decided among NBP. Among the DBP we analyzed if the biopsy resulted from a craniotomy or a stereotactic biopsy, and if there were procedural complications.

Diagnostic: Known history of cancer (prior to the diagnostic visit), infectious endocarditis or multiple sclerosis; type of imaging used for

***Corresponding author:** Gabriel M Aisenberg, Assistant Professor of Medicine, Division of Internal Medicine, University of Texas Health Science Center,Houston, USA, Tel: 713-500-6714; Fax:713-500-6722; E-mail:Gabriel.M.Aisenberg@uth.tmc.edu

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diagnosis of the lesion (CT, MRI), and several descriptive factors such as single versus multiple lesion, size, midline shift; location and uni- versus bi-laterality, degree of tissue involvement (extra axial, cortical-lesions not deeper than 1 cm from the pial surface-, and subcortical-lesions deeper than 1 cm from the pial surface), and the degree of gadolinium enhancement when available. Both groups were queried to determine if the following studies were performed and their rate of positivity: blood cultures, HIV serology (chemo luminescence; Siemens Centaur). If positive, we also analyzed CD4 count (flow cytometry B/D Canto II) as well as Epstein-Barr virus cerebrospinal fluid (CSF) analysis (PCR Roche light cycler). We assessed the request for serologies for brucellosis (EIA), borreliosis (EIA), Chagas (EIA), toxoplasmosis (chemo luminescence; Siemens Centaur) and syphilis (RPR: Serodia, and TPPA: Cardinal), angiotensin converting enzyme (ACE) levels (Kinetic); PPD and Quantiferon gold (ELISA), and in the cases with final diagnosis of neurocysticercosis, the use of specific serology (EIA); we analyzed the use of genetic markers in biopsy or serum, the search for abnormalities in the cerebrospinal fluid (CSF) markers such as glucose, proteins, white cell count and its differential, and oligoclonal bands; and finally the use of extra-cerebral images such as chest X ray and computed tomography of chest/abdomen/pelvis.

We included as final diagnoses those resulting from the biopsy within the DBP group, and the diagnosis considered in the discharge note when available, or the neurology/neurosurgery note in the NBP group. The diagnoses were divided in the following categories: primary brain tumor, metastases, vascular, infectious, demyelinating disorder, inflammatory, and miscellanea.

Statistical analysis

We used SPSS version 21 for the statistical analysis. Categorical variables were analyzed using the Fisher exact test, and discrete variables were analyzed using the Student t test for unpaired samples. A logistic regression model was used to compare the association of discrete and continuous variables with the probability of having a brain biopsy. A two-sided $P < 0.05$ was considered indicative of statistical significance.

Results

Forty patients with a brain or cerebellar biopsy with diagnostic intention (DBP), and 272 patients without a biopsy (NBP) were included. Baseline characteristics are presented in Table 1.

Brain biopsy was less frequently obtained from patients with history of cancer or multiple sclerosis, those with frontal or occipital lesions, those with lesions affecting both sides of the cerebrum or cerebellum, and those with subcortical lesions or with homogeneous contrast enhancement. Patients presenting with motor deficit, decreased mentation (confusion/coma), single brain lesions, larger than 3 cm, with midline shift, or with complete ring enhancement with gadolinium were more frequently biopsied. As it might be expected, biopsied patients were more frequently admitted, with longer hospitalizations, and had significantly more brain CT and MRI studies.

Of the 40 biopsied patients, 8 had diagnostic stereotactic biopsies (one additional was non diagnostic; the patient then required a craniotomy) and 32 had a craniotomy. After the craniotomy three patients developed complications (2 acquired hydrocephalus and one had seizures). None of the patients whose biopsy was stereotactic experienced complications. In our series, the selection of stereotactic biopsy versus craniotomy was not significantly associated with lesion location, size, or type of gadolinium enhancement.

Among non-biopsied patients the median time from lesion-finding to treatment initiation when indicated was 8 ± 44 days. Intervention was not indicated in 117 patients (43%) of the NBP group, either because of their underlying severe comorbidities, or because the decision was to observe the natural course of the found lesion.

The following variables were entered into a logistic regression model based on the findings in Table 1: history of cancer with potential for brain metastasis, motor deficit, confusion or coma, presence of a single brain lesion, lesion bigger than 3 cm, midline shift, bilateral lesion, subcortical lesion, and complete ring gadolinium enhancement. History of cancer was negatively associated with the probability of brain biopsy (OR=0.135, 95% CI 0.045-0.404, $P<0.001$), whereas the presence of motor deficit (OR=3.964, 95% CI 1.549-10.143, $P=0.004$) and lesions bigger than 3 cm (OR=4.862, 95% CI 1.601-14.770, $P=0.005$) increased that probability.

Table 2 shows the pathologic diagnoses of the 40 DBP and the presumed diagnoses of the 272 NBP.

Table 3 shows the studies performed among biopsied and not biopsied patients, as well as their positivity rate. More DBP had chest films than NBP, though this might have been for operative preparation. Consistent with this hypothesis the positivity rate for chest X ray and CT of the chest, abdomen and pelvis is significantly higher for NBP than that of DBP.

Overall the number of cerebrospinal fluid, blood, genetic or immunologic tests requested on both groups was low, but more importantly, the positivity rate was very low. Those in DBP group had more frequent lumbar punctures, toxoplasma serologies and Quantiferon tests, with no difference in the yield when compared with NBP.

Based on the data from Tables 1-3, we built a clinical path (Figure 1) used among our patients with a brain lesion, specifically with regard to intervention (biopsy versus treatment or observation).

The HIV positive patient

Seven HIV positive patients had diagnostic brain biopsies (17% of DBP). The diagnoses were toxoplasmosis in 4, progressive multifocal leukoencephalopathy (PML), primary central nervous system lymphoma and ischemic stroke in one each. Of the 4 patients with toxoplasmosis, 2 had classic ring enhancing lesions, 1 had incomplete-ring enhancement and the other an irregularly enhancing lesion. One had a single subcortical lesion, and the other 3 had multiple lesions (cortical in 1, subcortical in 1 and cortico-subcortical in 1). Two had focal motor deficit, and 1 presented with decreased mentation.

Eighteen (7%) of the 272 NBP were HIV positive. Their presumed diagnoses were toxoplasmosis in 9 patients, cavernous malformation, histoplasmosis, ischemic stroke, cryptococcosis, neurocysticercosis and progressive multifocal leukoencephalopathy in one each. Three patients had an abnormal brain image not otherwise specified. Among the 9 patients whose presumed diagnosis was toxoplasmosis, 4 had ring enhancing lesions, 3 had incomplete-ring enhancement, 1 had a cortical lesion, and 2 had no enhancement. Six of the patients had subcortical lesions, and 2 had cortico-subcortical lesions. Three presented with focal motor deficit and other 3 with decreased mentation. The lesions were bilateral in 4, and single in the other 4.

Table 1:Baseline characteristics of NBP and DBP.

	NOT BIOPSIED *n*=272	DIAGNOSTIC BIOPSIES *n=40*	*P*
Age (median ± stdev)	53 ± 12	51 ± 14	0.25
Gender (male)	117 (43%)	25 (62%)	**0.03**
Race			
Afro-American	87 (32%)	15 (37.5%)	0.48
Far-Asian	12 (4%)	1 (2.5%)	1.00
Hispanic	125 (46%)	19 (47.5%)	0.87
Middle Eastern	6 (2%)	1 (2.5%)	1.00
White	42 (15%)	4 (10%)	0.48
Admitted	179 (66%)	40 (100%)	**<0.001**
Average length of stay	6 ± 7 days	13 ± 15 days	**<0.001**
Known h/o cancer	180 (66%)	5 (12.5%)	**<0.001**
Known h/o MS	4 (1.5%)	0 (0%)	**0.008**
Symptoms/signs			
Headache	75 (28%)	11 (27.5%)	1.00
Motor deficit	56 (21%)	19 (47.5%)	**<0.001**
Sensitive deficit	36 (13%)	9 (17.5%)	0.15
Confusion/coma	34 (12%)	12 (30%)	**0.007**
Vomiting	25 (9%)	2 (5%)	0.55
Seizures	28 (10%)	6 (15%)	0.40
Hypertension	2 (0.75%)	0 (0%)	1.00
CT head done	234 (86%)	40 (100%)	**0.007**
MRI done	197 (72%)	36 (90%)	**0.02**
EEG done	0 (0%)	0 (0%)	1.00
Single lesion	113 (42%)	28 (70%)	**0.001**
Larger than 3 cm	26 (10%)	20 (50%)	**<0.001**
Midline shift	25 (10%)	14 (35%)	**<0.001**
Location (per area)			
Frontal	155 (57%)	14 (35%)	**0.01**
Temporal	63 (23%)	15 (37.5%)	0.08
Parietal	131 (48%)	14 (35%)	0.13
Occipital	73 (27%)	2 (5%)	**0.001**
Cerebellar	92 (34%)	8 (20%)	0.1
Pons	30 (11%)	3 (7.5%)	0.78
Bilateral	124 (46%)	7 (17.5%)	**<0.001**
Location (per depth)			
Extra axial	57 (21%)	8 (20%)	1.00
Cortical	163 (61%)	22 (55%)	0.49
Subcortical	177 (66%)	19 (48%)	**0.03**
Meningeal	42 (16%)	11 (28%)	0.07
Gadolinium enhancement			
Nodular	16 (6%)	3 (8%)	0.72
Complete ring	63 (24%)	17 (43%)	**0.02**
Incomplete ring	20 (7%)	2 (5%)	0.75
Irregular	133 (50%)	19 (48%)	0.87
Homogeneous	106 (40%)	8 (20%)	**0.02**

The comparison of their baseline characteristics, clinical presentation, mass features, and studies performed and positivity rate is presented on Table 4. Even though more RPR/TPPA or toxoplasmosis serologies were requested among NBP, the rate of positivity was similar in both groups. Masses larger than 3 cm increased the chance of biopsy but not significantly. Notice that the predictors for biopsy present in the general population don't appear among the HIV positive patients.

All the HIV positive DBP whose final diagnosis was toxoplasmosis (*n*=4) were treated for that infection before biopsy for 14 days. Three of these 4 patients had positive toxoplasma serology. The 3 patients with a different diagnosis were also empirically treated for toxoplasmosis for 9 days. Among the NBP, the 9 patients with presumed diagnosis of toxoplasmosis were treated for that infection (6 had serology for toxoplasmosis tested, with positive results in 5). Three other patients were treated for toxoplasmosis, although their presumed diagnoses were different.

Discussion

To our knowledge this is the first study that evaluates doctors' attitude towards the presence of a brain lesion regardless of the presumed diagnosis, leading to observation, biopsy or treatment. Overall, motor deficit, confusion or coma, single brain lesion, larger than 3 cm, with midline shift and complete ring enhancement made brain biopsy more likely, whereas bilateral brain or cerebellar lesion, presence of subcortical lesions with homogeneous enhancement, and history of cancer with potential for brain metastases made the biopsy less likely. We also observed that the laboratory tests evaluated were inadequate surrogates of brain histology, whereas abnormalities on chest X ray or CT of the chest, abdomen or pelvis made the probability of brain biopsy lower.

Our patients were found to have lesions after presenting with neurologic deficit, altered mental status or headache, or when CT of the brain was part of the staging of underlying malignant diseases.

Tumors

About 15% of patients dying from cancer have brain parenchymal metastases. In 70-75% of them there is more than one lesion [12]. The symptoms of brain lesions depend on location and size. The most sensitive neuroimages (CT and MRI) are capable of finding lesions 5 mm and bigger [13]. Ring-enhancement following gadolinium administration can be seen in some infections and also in glioblastoma and solitary brain metastasis [14]. Fluorodeoxy glucose Positron-Emission Tomography (FDG-PET) scans display different enhancing patterns in lymphoma in comparison with high-grade glioma or brain metastases, but can't replace tissue analysis [15]. The combination of functional MRI and PET can predict some outcome variables in meningioma; however, histology is still needed to establish diagnosis. Extra-axial meningiomas, granulomas and cysts share similar clinical syndromes and a slow growth rate that allow repeated neuroimaging rather than a biopsy for their diagnostic approach [16]. In our series 50% of the biopsied patients had either primary or metastatic tumors, whereas those categories represented 80% of NBP. This enhances the value of non-invasive means for decision-making on patients affected by primary or secondary tumors.

Multiple sclerosis

In our series patients with multiple sclerosis (MS) were uncommon. The need for biopsy in MS seems infrequent in the setting of the "typical" clinical picture. Since 2001 the diagnosis of MS relies upon "typical" MRI findings in the proper clinical setting [17]. Additionally, CSF markers including increased IgG index, IgG synthesis rate or the presence of oligoclonal bands have been reported in up to 90% of patients with MS and is commonly used to establish diagnosis [18]. Tumefactive MS, defined as tumor-like demyelinating areas greater than two centimeters, differs clinically from "typical" MS, and may resemble neoplasms. This presentation accounts for 1-2 per 1000 cases of MS, and due to tumor-like presentation it's more likely to lead to brain biopsy [19].

Table 2: Diagnoses For The 312 Patients.

	DIAGNOSTIC CATEGORY	N	DIAGNOSIS	N	SB
BIOPSIED PATIENTS (N=40)	PRIMARY BRAIN TUMOR	13	GLIOBLASTOMA MULTIFORME	5	3
			ANAPLASTIC ASTROCYTOMA	3	3
			PRIMARY CNS LYMPHOMA	3	
			INFILTRATING GLIOMA NOS	1	1
			MENINGIOMA	1	
	INFECTIOUS	12	TOXOPLASMOSIS	4	1
			BRAIN ABSCESS	3	
			NEUROCYSTICERCOSIS	3	
			POST INFECTIOUS LEUKOENCEPHALITIS	1	
			PML	1	
	METASTATIC CANCER	7	METASTATIC BREAST CANCER	2	1
			METASTATIC LUNG CANCER	2	1
			METASTATIC CARCINOMA NOS	1	
			METASTATIC COLON CANCER	1	
			METASTATIC SARCOMA	1	
	VASCULAR LESION	4	BRAIN INFARCT	3	
			CAVERNOUS MALFORMATION	1	
	INFLAMMATORY	2	EOSINOPHILIC VASCULITIS	1	
			WHIPPLE'S DISEASE	1	1
	DEMYELINATING DISEASE	1	MULTIPLE SCLEROSIS	1	
	MISCELLANEA	1	GLIOSIS	1	1
NOT BIOPSIED PATIENTS (N=272	METASTATIC CANCER	178	METASTATIC LUNG CANCER	88	
			METASTATIC BREAST CANCER	52	
			METASTATIC COLON CANCER	6	
			METASTATIC MELANOMA	4	
			UNKNOWN PRIMARY METASTASIS	4	
			METASTATIC ESOPHAGEAL CANCER	3	
			METASTATIC RENAL CANCER	3	
			METASTATIC UTERINE CANCER	3	
			METASTATIC NEUROENDOCRINE TUMOR	2	
			METASTATIC PROSTATE CANCER	2	
			METASTATIC SARCOMA	2	
			METASTATIC TESTICULAR CANCER	2	
			METASTATIC BLADDER CANCER	1	
			METASTATIC CHORIOCARCINOMA	1	
			METASTATIC ENDOMETRIAL CANCER	1	
			METASTATIC GASTRIC CANCER	1	
			METASTATIC LARYNGEAL CANCER	1	
			METASTATIC THYMIC CANCER	1	
			METASTATIC THYROID CANCER	1	
	PRIMARY BRAIN TUMOR	38	MENINGIOMA	29	
			SCHWANNOMA	4	
			HEMANGIOBLASTOMA - VHL	2	
			ASTROCYTOMA	1	
			EPENDYMOMA	1	
			GLIOBLASTOMA	1	
	INFECTIOUS	27	TOXOPLASMOSIS	9	
			NEUROCYSTICERCOSIS	8	
			BRAIN ABSCESS	5	
			CRYPTO MENINGITIS; UNKONWN MASS	1	
			DISSEMINATED COCCIDIOIDOMYCOSIS	1	
			HISPTOPLASMOSIS	1	
			PML	1	
			TUBERCULOMA	1	
	MISCELANEA	11	BRAIN MASS NOT OTHERWISE SPECIFIED	11	
	VASCULAR LESION	11	CAVERNOUS MALFORMATION	9	
			ISCHEMIC STROKE	2	
	DEMYELINATING DISEASE	5	MULTIPLE SCLEROSIS	5	
	MISCELLANEA	2	ARACHNOID CYST	1	
			DERMOID CYST	1	
NOS: Not Otherwise Specified; SB: Stereotactic Biopsy					

Table 3: Studies performed among biopsied and not biopsied patients, and their positivity.

	BIOPSIED				NOT BIOPSIED				*P*	*P*
	***n*=40**				***n*=272**				**(studies)**	**(positive results)**
	n	**%**	**positive**	**%**	***n***	**%**	**positive**	**%**		
Blood tests										
Cultures	14	35%	0	0	60	22%	5	8%	0.08	0.58
HIV serology	29	73%	7	24%	156	57%	18	12%	0.08	0.08
CD4 count (median ± SD) #	15 ± 51				41 ± 253				0.19	
Brucella serology	1	3%	0	0%	2	1%	0	0%	0.34	1.00
Borrelia serology	0	0%	n/a		0	0%	n/a		1.00	n/a
Chagas serology	0	0%	n/a		0	0%	n/a		1.00	n/a
RPR or TPPA	7	18%	1	14%	39	14%	3	8%	0.63	0.50
Toxoplasma serology	9	23%	3	50%	25	9%	12	48%	**0.02**	0.70
Cysticercosis serology *	0	0%	n/a		1	14%	1	100%	1.00	1.00
ACE levels	2	5%	0	0%	3	1%	0	0%	0.12	1.00
Quantiferon gold	5	13%	0	0%	8	3%	2	33%	**0.02**	0.49
Genetic tests	1	3%	0	0%	6	2%	2	33%	1.00	1.00
Immunologic tests										
PPD test	1	3%	1	100%	2	1%	1	50%	0.34	1.00
Lumbar puncture										
Oligoclonal bands	2	5%	0	0%	3	1%	2	67%	0.12	0.40
Other CSF studies	13	33%	9	69%	28	10%	15	54%	**<0.001**	0.50
EBV PCR in CSF#	5	71%	2	40%	6	33%	0	0%	0.18	0.18
Imaging										
Chest X ray	33	83%	6	18%	149	55%	94	63%	**<0.001**	**<0.001**
CT chest/abdomen/pelvis	22	55%	10	45%	164	60%	146	89%	0.50	**<0.001**

(*) only evaluated among patients whose final diagnosis was neurocysticercosis

(#) only evaluated among patients with diagnosis of HIV/AIDS

Infections

Ten percent of DBP had diagnoses of infectious diseases, whereas 15% of NBP had that category of presumed final diagnosis. Tuberculosis affects the neurological tissue in 2-5% of patients, and up to 10% of those HIV positive, causing meningitis more commonly than tuberculoma [20]. Since both represent forms of extrapulmonary tuberculosis suspicion of this diagnosis is key in absence of concomitant pulmonary involvement. Extraneural synchronous infection is present in about half of the patients; therefore, the association of proven tuberculosis and an intracranial lesion makes that lesion more suspicious for tuberculoma. Some studies found that AIDS is a risk factor and should increase the suspicion [21]. Most cases of tuberculoma are silent until meningitis supervenes [22]. The sensitivity of CSF acid-fast is 5-30%, and that of CSF culture 45% [23]. Interferon gamma assays from CSF samples, and DNA amplification by PCR (poor sensitivity but high specificity) do not increase the diagnostic ability [24]. Different groups found contradictory results on the accuracy of adenosine deaminase CSF levels for the diagnosis of neurological tuberculous involvement [25-27]. Only one patient in the NBP group was suspected to have a neuro-tuberculoma, on the basis of abnormal chest film, brain images, positive PPD and interferon gamma assay in blood. Neuroimaging lacks diagnostic specificity in CNS tuberculosis. The same happens in the case of syphilitic gumma [28,29] and neurobrucellosis [30], two infrequent causes of infectious masses. Lyme disease can be associated with neurologic involvement but masses are not described [31]. In spite of the reported low sensitivity and specificity of the above tests, many of our patients had them checked.

In patients with hematological malignancies, AIDS or organ transplant, Chagas disease can present with multiple necrotizing brain lesions, some pseudotumoral (chagoma) resulting from reactivation of previous infection. A positive serology is not enough proof of reactivation; CSF examination seldom yields a parasitic diagnosis, and images are non-specific. Occasionally the use of stereotactic biopsy becomes necessary, though some authors recommend a "treat and reassess" approach, similar to the one of cerebral toxoplasmosis [32]. Analysis of blood and CSF samples is also deemed less accurate than tissue biopsy and culture in the evaluation of other suspected protozoal brain infections [33]. In neurocysticercosis the diagnosis rests on a combination of epidemiological, clinical, laboratory and images data. For the dubious active case there is a role for brain biopsy [34].

In our patient population cerebral toxoplasmosis was relatively uncommon. The presumptive diagnosis is based on the combination of neurologic deficit, contrast-enhancing lesions on CT or MRI, and successful response to 2 weeks of specific treatment [35]. Our patients' images showed ring enhancement in 6 of the 12 cases, and the presence of focal neurologic deficit happened in just 5 patients.

In HIV positive patients the finding of Epstein-Barr viral (EBV) DNA by PCR in the cerebrospinal fluid (CSF) is sensitive in the diagnosis of patients whose brain mass is caused by central nervous system (CNS) lymphoma. One of our 3 patients with primary CNS lymphoma was HIV positive, with a very low CD4 count, and a positive PCR for EBV in the CSF. In absence of a brain lesion the positive predictive value for CNS lymphoma of EBV PCR in CSF is 10% [36]. The tumors in CNS lymphoma can affect the brain, meninges, spinal cord and optic nerves, or can lie out of the CNS in 12%. Although the combination of clinical and ophthalmological examination, contrast MRI and HIV positive status improve the predictive value for CNS lymphoma, the standard diagnostic test is the brain biopsy [37].

The diagnosis of PML, a viral opportunistic demyelinating infectious disease, can be suggested by MRI. In one of our NBP

Table 4: Characteristics of HIV positive DBP and NBP

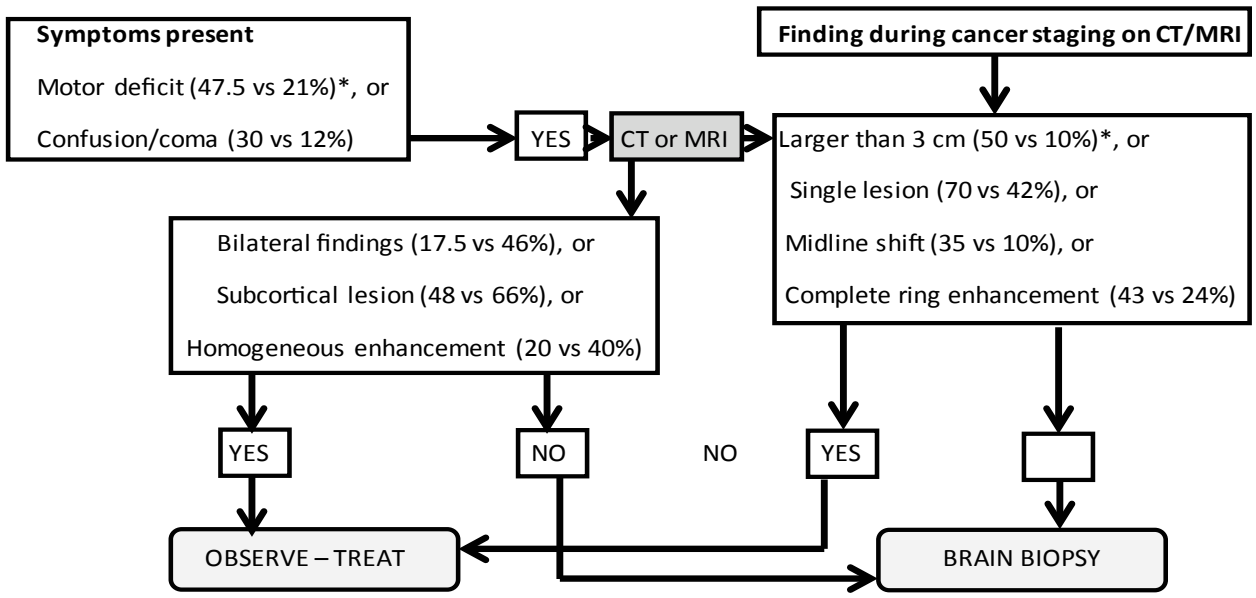
	NOT BIOPSIED PATIENTS	BIOPSIED PATIENTS	*P*
	n=18	*n*=7	
Age (median ± SD)	37 ± 8	36 ± 8	0.71
Male gender (%)	10 (56%)	5 (71%)	0.66
Admitted	15 (83%)	7 (100%)	0.53
LOS (median ± SD)	8 ± 12	18 ± 9	0.30
history of cancer	0 (0%)	0 (0%)	1.00
symptoms			
headache	4 (22%)	1 (14%)	1.00
focal motor	5 (28%)	3 (43%)	0.64
focal sensitive	2 (11%)	0 (0%)	1.00
confusion/coma	6 (33%)	2 (29%)	1.00
vomiting	1 (6%)	0 (0%)	1.00
HTN	0 (0%)	0 (0%)	1.00
seizures	1 (6%)	1 (14%)	0.49
studies			
CT head	17 (94%)	7 (100%)	1.00
MRI head	17 (94%)	5 (71%)	0.18
single image	11 (61%)	5 (71%)	1.00
>3 cm	1 (6%)	3 (43%)	0.05
midline shift	1 (6%)	2 (29%)	0.18
bilateral image	5 (28%)	2 (29%)	1.00
blood cultures	9 (50%)	4 (57%)	1.00
positive	2 (22%)	0 (0%)	1.00
brucella serology	1 (6%)	0 (0%)	1.00
positive	0 (0%)	0 (0%)	1.00
chagas serology	0 (0%)	0 (0%)	1.00
positive	0 (0%)	0 (0%)	1.00
borrelia serology	0 (0%)	0 (0%)	1.00
positive	0 (0%)	0 (0%)	1.00
toxoplasmosis	17 (94%)	3 (43%)	**0.01**
positive	10 (59%)	0 (0%)	0.21
RPR/TPPA	16 (89%)	2 (29%)	**0.01**
positive	1 (6%)	1 (50%)	0.22
quantiferon gold	1 (6%)	1 (14%)	0.49
positive	0 (0%)	0 (0%)	1.00
CSF studies	9 (50%)	3 (43%)	1.00
positive	5 (56%)	3 (100%)	0.49
CT chest/abd/pelvis	3 (17%)	2 (29%)	0.60
positive	2 (67%)	1 (50%)	1.00
chest X ray	14 (78%)	3 (43%)	0.16
positive	3 (21%)	1 (33%)	1.00
EBV in CSF	6 (33%)	3 (43%)	0.68
positive	0 (0%)	2 (67%)	0.08
CD4 (median ± SD)	52 ± 258	15 ± 51	0.18
Toxottx tried	11 (61%)	3 (43%)	0.66
Time to intervention (days)*	11 ± 27	27 ± 65	0.09

* (either biopsy or change of plan)

patients with HIV and 228 CD4/μl, the MRI supported the presumed diagnosis. The biopsied patient with this diagnosis had AIDS and 19 CD4/μl. Older studies state that the sensitivity of CSF PCR for the causative agent, JC virus is poor even repeating the samples, making brain biopsy the confirmatory test [35]. New evidence suggests an increased sensitivity and specificity of new PCR techniques, advocating avoidance of biopsy in the right clinical setting [38].

Stereotactic biopsy

This minimally invasive procedure carries a diagnostic yield from 85 to 98%, complication rates from 2 to 6.5% [39]. As more experience is collected by the use of this method, new recommendations encourage doctors to repeat the stereotactic procedure when the results are non-diagnostic over the alternatives (empirical treatments or open craniotomy) [40].



MODIFIERS THAT DID NOT ALTER THE CHANCE OF BIOPSY	MODIFIERS THAT DECREASED THE CHANCE OF BIOPSY
Blood cultures (0 vs 8%)	History of cancer (12.5 vs 66%)*, or
HIV serology (24 vs 12%)	Abnormal chest X ray (18 vs 63%), or
Brucella serology (0 vs 0%)	Abnormal CT chest/abd/pelvis (45 vs 89%)
RPR or TPPA (14 vs 8%)	
ACE levels (0 vs 0%)	
Chagas serology (0 vs 0%)	
Toxoplasma serology (50 vs 48%)	
PPD test (100 vs 50%)	
Borrelia serology (0 vs 0%)	
Quantiferon Gold (0 vs 33%)	
EBV PCR in CSF of HIV patients (40 vs 0%)	
CSF general studies (69 vs 54%)	
CSF oligoclonal bands (0 vs 67%)	

Percentages are DBP versus NBP

* : statistically significant difference after multivariate analysis

Figure 1: Clinical path used among our patients with a brain lesion, specifically with regard to intervention (biopsy versus treatment or observation).

The retrospective nature of our study constitutes its main limitation; we cannot clearly determine why the decision to biopsy or not was made, nor why certain studies were ordered. Therefore, the association between laboratory or imaging findings and the probability of biopsy or alternative intervention is not necessarily causal. Moreover, certain variables of interest (example: eloquent versus non-eloquent cortex, or other modalities of imaging not regularly available in our center) limit our ability to generalize our findings. We intend to prospectively validate the clinical path described in Figure 1, promoting the use of stereotactic biopsy as a gold standard to adequately determine sensitivity and specificity of the above-mentioned laboratory and imaging tests.

A second limitation of our study is the fact that the data is originated in a 2-center single institution; however, to our knowledge there is no larger data set in the literature.

Conclusions

In our large population of patients with brain lesions diagnostic biopsy was a relatively uncommon occurrence. Patients with lesions larger than 3 cm in diameter and those presenting with focal neurologic deficit were more likely to be biopsied, while the strongest predictor against biopsy was the history of cancer with potential for brain metastasis. The path from lesion finding to the decision to observe, to treat or to biopsy was heterogeneous. Among the biopsied patients multiple laboratory or imaging interventions did not modify the need for the biopsy. The predictors for biopsy were not present

among our HIV positive patients. It would be relevant to compare our findings with data generated in different medical settings (private hospitals, other cities) in order to be able to create a more homogeneous approach to the patient with brain lesion.

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Author Affiliations

Top

[1]*Division of Internal Medicine, University of Texas Health Science Center, Houston, USA*
[2]*Division of Neurology, University of Texas Health Science Center, USA*
[3]*Division of Radiology, Baylor College of Medicine, USA*
[4]*Division of Neurosurgery, University of Texas Health Science Center, USA*
[5]*Division of Clinical Research, University of Texas Health Science Center, USA*