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ORIGINAL ARTICLE - NEUROSURGERY GENERAL

Brain biopsy in suspected non-neoplastic neurological disease

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Abstract

Brain biopsy has a well-established role in the diagnosis of CNS neoplasia. Nevertheless, despite being essential for the diagnosis of some benign neurological diseases, little consensus exists regarding its indications for disease diagnosis and patient orientation. Our aim was to assess brain biopsy diagnostic yield in patients with neurological deterioration of unknown etiology, to identify the clinical characteristics associated with an increased likelihood of achieving a diagnostic biopsy as well as the characteristics linked to a particular diagnosis.

Methods A retrospective analysis of 62 consecutive brain biopsies performed at a single tertiary care center between January 2004 and December 2015 for suspected non-neoplastic neurological disease was performed. The clinical presentation, imaging, and laboratory results were collected and compared between diagnostic groups.

Results Sixty-eight percent of the biopsies led to a definitive diagnosis. The most common histological diagnosis was central nervous system lymphoma (eight cases), followed by astrocytoma, demyelinating disease, and progressive multifocal leukoencephalopathy (four cases each). No clinical characteristics were found to predict a diagnostic biopsy or to correlate with a specific diagnosis. Importantly, a distinct diagnosis from the initially suspected was achieved in 52% of cases and biopsy findings led to a change of therapeutic orientation in 78% of the cases.

Conclusions Our results suggest that brain biopsies have a significant impact on patient management and should be considered early in selected cases in which less invasive testing was unable to reach a definitive diagnosis.

Keywords Brain biopsy · Benign neurological disease

Abbreviations

ADC	Apparent diffusion coefficient
AIDS	Acquired immunodeficiency syndrome
CNS	Central nervous system
CSF	Cerebral spinal fluid
CT	Computed tomography
DWI	Diffusion weighted imaging
FLAIR	Fluid-attenuated inversion recovery
HBV	Hepatitis virus B
HCV	Hepatitis C virus
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
MRI	Magnetic resonance imaging
PML	Progressive multifocal leukoencephalopathy

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Introduction

The unraveling of the pathophysiology of neurological diseases has led to the identification of putative targets for pharmacological treatment. Advances in imaging techniques enabled a crucial evolution in the understanding and characterization of these diseases, while refining the imaging criteria related to a diagnosis. Nevertheless, although clinical, laboratory testing, and imaging may point toward a certain diagnosis, such promise for disease-modifying interventions raises the need for a definite and precise diagnosis. Tissue analysis is still the mainstay for the diagnosis, particularly in atypical cases.

Brain biopsies are a well-established diagnostic option in brain tumor cases, with a reported sensitivity ranging from 62 to 95% [8, 10, 13]. However, in non-neoplastic neurological disease, no consensus exists regarding the indications or the appropriate timing for brain biopsy. Most often, it is only considered as a last resort in rapidly progressive cases or in atypical conditions in which the differential diagnosis includes potential treatable diseases [4, 11, 21].

Empirically, brain biopsies are commonly thought as having a low diagnostic yield for neurological diseases. This idea is probably maintained as literature presents a wide range of contrasting results. Diagnostic yields described range from as low as 20 up to 83% [4, 5, 11, 12, 21, 22]. Moreover, conclusions on clinical orientation benefit and patient outcome are divergent. Some studies show little influence on management associated with little therapeutical benefit, while others show a significant impact on patient management and outcome [12, 19, 22]. Of note, Gilkes et al. reviewed published series investigating the value of brain biopsy in neurological disease and highlighted the disparities in selection and inclusion criteria among these studies, as well as heterogeneity in biopsy quality, standard of neuropathology, and microbiology studies. These differences ultimately may underlie the wide variation in diagnostic yields and associated conclusions described among studies [7].

Brain biopsy is an invasive option and should therefore only be considered when significant benefit surpasses the risk of inducing harm. However, scarce information exists as how to infer this ratio from clinical presentation, primary clinical suspicion, imaging, and other complimentary exam results [17]. Important questions remain to be determined, including the acceptable waiting period until the decision for brain biopsy in undiagnosed, possibly treatable cases.

Considering the lack of clinical evidence in guiding biopsy decision in such cases, we have reviewed our series of consecutive brain biopsies performed for suspicion of benign neurological disease. Our primary goal was to determine diagnostic yield of brain biopsy. Secondary end points include evaluation of impact on patient management, as well as identification of demographic, clinical, and imaging characteristics more likely to increase the chance of achieving a diagnostic biopsy or associated with a specific diagnosis.

Materials and methods

We performed a retrospective analysis of 62 consecutive adult patients who underwent brain biopsy for neurological disease of unknown etiology at a tertiary medical center, Centro Hospitalar Universitário do Porto, between January 2004 and December 2015.

Indications for brain biopsy included:

- Rapid neurologic decline of unknown etiology;
- Atypical presentation of cognitive decline;
- Inflammatory disease or vasculopathy suspicion without clinical or laboratory criteria for diagnosis;
- Treatment failure for most likely diagnosis in HIV patients.

We reviewed clinical details and biochemical, microbiology, CSF, brain MRI, and brain biopsy findings for each case. The main diagnostic hypothesis and treatment before and after biopsy, as well as biopsy complications, were also included in the analysis.

Patients under the age of 18 years or with history of refractory epilepsy were excluded, as well as patients with the most likely diagnosis of a neoplastic lesion, including lymphomatous neoplasm. Patients with incomplete clinical, laboratory, or imaging data were excluded. Repeated biopsies were included only with the diagnostic biopsy data.

Imaging studies (CT and MRI) were conducted and evaluated by a neuroradiologist at our hospital and brain biopsy samples by a neuropathologist (either RT or MP). Thirty patients had also their brain biopsy samples evaluated through microbiology studies.

The demographics and presenting signs and symptoms were analyzed and compared between groups in order to identify characteristics more likely to yield a certain diagnosis.

Univariate and multivariate analyses were performed to determine which clinical and imaging parameters predict a diagnostic brain biopsy (Wizard 1.8.15).

Results

Management algorithm

The decision to proceed to brain biopsy was patient based in all cases.

Nevertheless, a common algorithm could be retrospectively identified at our institution (Fig. 1). Importantly, the list of tests and investigations was not considered a checklist and

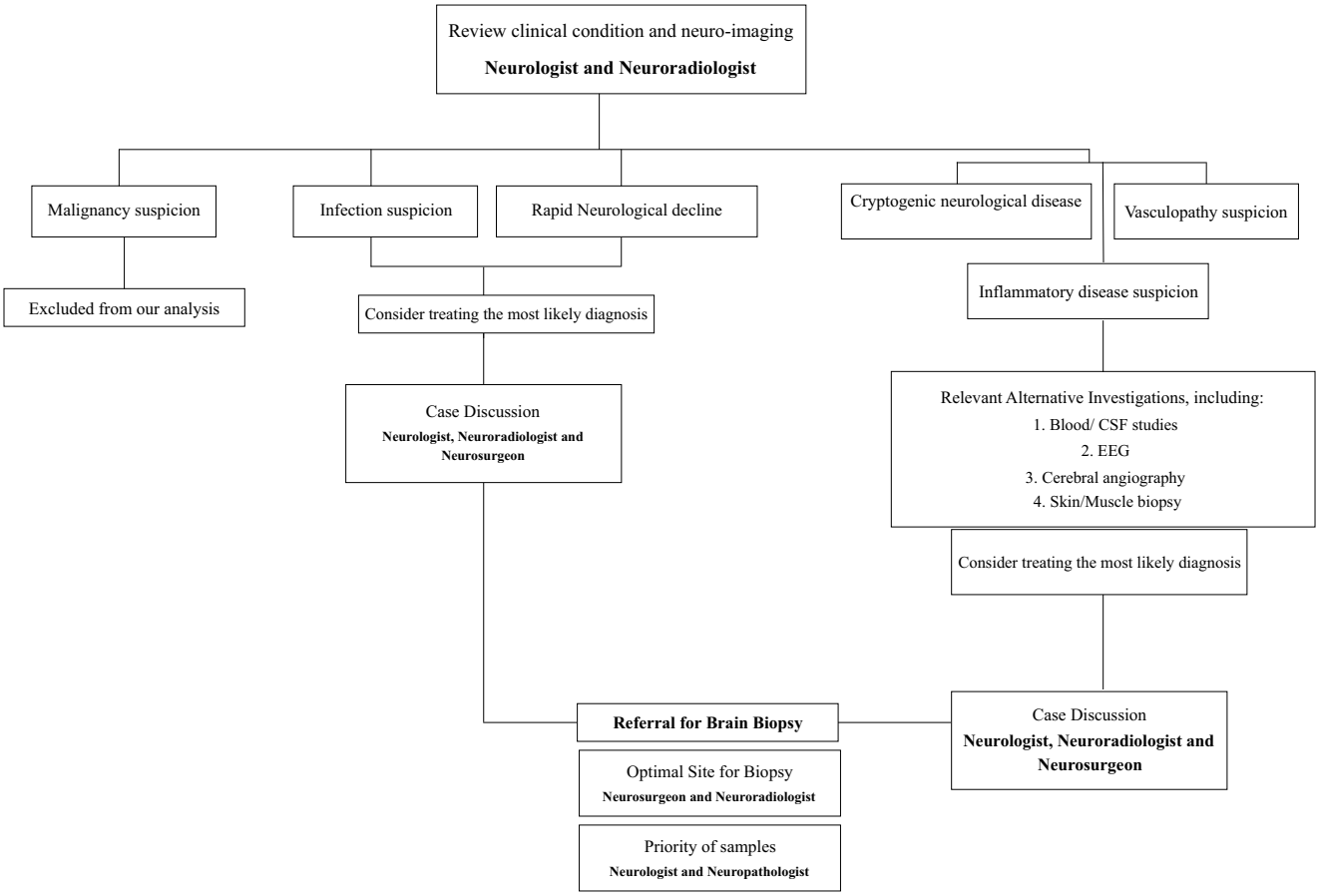

Fig. 1 Decision algorithm for brain biopsy referral at our institution

was only pursued when considered relevant for each case. Moreover, in time-sensitive cases, as those presenting with rapid neurologic deterioration, an expeditious decision to undergo biopsy was met.

Clinical characteristics

The present study involved 62 patients: 26 females and 36 males. At the time of the biopsy, patient age ranged between 20 to 79 years with an average of 53.016 (± 3.649, SD).

The main presenting signs and symptoms are described in Table 1 and were divided into six groups: behavioral/psychiatric changes, cognitive decline, seizures, focal neurological signs, headache, and encephalopathy. Focal neurologic signs were the most common presentation, including motor deficits and speech disturbances in 29 patients (46.8%).

We further evaluated the association between neuropathological diagnosis and clinical presentation (Table 2). In order to do so, we considered all presenting signs and symptoms for a given patient.

There were no significant differences in diagnostic yield when taking the clinical presentation into account (Table 1); we did not find an expressive association between clinical presentation and histopathological diagnosis. Nevertheless, in our series, presentation with seizures was most frequent in patient with vasculopathy, while absent in patients with PML (Table 2).

Symptom duration ranged between 5 days to 10 years. Most patients had a duration of months between first manifestation and biopsy date; 85% of patients had symptoms for less than 1 year. The duration of symptoms equals time until referral for brain biopsy. Time between symptom onset and referral was related to the nature and severity of the initial symptoms. The referral was deferred in a small number of patients (12 patients) due to attempted treatment for the most probable cause of brain lesion, being the biopsy considered only for non-responsive patients.

Systemic features were identified in 18 patients (29%) (Table 1). Fever and laboratory inflammatory parameters (erythrocyte sedimentation rate and C-reactive protein) were not found to be markers for infectious CNS disease in our sample and were considered unspecific inflammatory markers.

Three patients underwent chemotherapy and one patient had a previous liver transplant. Importantly, 19 immunocompromised patients were included in our analysis, of which 11 were HIV positive. The characteristics of HIV patients, including ongoing treatment, clinical presentation, and imaging characteristics, are summarized in Table 3 and will be discussed below.

Table 1 Demographics and clinical characteristics of the individuals submitted to brain biopsy and correlation to diagnosis

Clinical details	Number by category	Mean (range)	Number of diagnosis	Percent of diagnosis	P
Gender					0.851
Female	26		18	69	
Male	36		24	66.6	
Age		53 (20–79)			0.901
Clinical presentation					0.244
Behavioral changes	11		6	55	0.310
Cognitive decline	8		3	38	0.0510
Encephalopathy	1		1	100	0.495
Focal neurological signs	29		22	76	0.206
Headache	2		2	100	0.329
Seizures	11		8	73	0.702
Duration					0.013
< 2 weeks	6		3	50	0.058
< 2 month	20		15	75	0.138
< 1 year	27		21	78	0.154
> 1 year	9		3	33	0.017
Systemic features					0.785
Auto-immune disease	3		3	100	0.227
Chemotherapy	3		2	67	0.968
Fever	3		2	67	0.763
HIV	11		7	64	0.495
Primary immunodeficiency	1		1	100	0.541
Transplant	1		1	100	0.053
Corticoid therapy					0.053
Yes	23		20	87	0.052
No	39		22	56	0.052
MRI					0.014
Diffuse changes	11		4	36	0.014
Focal/multifocal lesions	51		38	75	0.014
Biopsy					0.272
Stereotactic	37		27	73	0.291
Neuronavigation	11		8	73	0.702
Open	14		7	50	0.110

Twenty-three patients were treated with steroids prior to the biopsy, and this treatment did not seem to influence the final diagnosis. Only one patient treated with steroids remained without neuropathological diagnosis, which had diffuse changes on MRI and follow-up upon corticoid withdrawal did not show disease progression.

Although withdrawal or deferred corticoid therapy is done when possible at our center according to biopsy referral, in this cohort patients with diagnostic suspicion of lymphoma were excluded from the analysis. Interestingly, three out of eight patients diagnosed with lymphoma received high-dose corticotherapy as the initial clinical diagnosis was a demyelinating disease.

Other diagnostic tests

Computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients. MRI sequences included T1, T1, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), apparent-diffusion coefficient (ADC), and gadolinium enhancement when available. Spectroscopy (12/62 patients) and MRI perfusion (20/62 patients) were only occasionally performed in our cohort.

We differentiated MRI findings into focal lesion or diffuse changes. Diffuse changes were codified when only diffuse signal changes in cerebral parenchyma or atrophy were

Table 2 Neuropathological diagnosis considering clinical presentation

	Number of biopsies	Behavioral changes (%)	*p*	Cognitive decline (%)	*p*	Encephalopathy (%)	*p*	Focal neurological signs (%)	*p*	Headache (%)	*p*	Seizures (%)	*p*
SNC infection	9	11	0.690	22	0.690	0	0.708	77	0.174	11	0.690	11	0.827
Lymphoma	8	25	0.415	75	0.061	0	0.708	62.5	0.174	12.5	0.690	12.5	0.827
Vasculopathy	6	0	0.061	83	0.415	16	0.003	50	0.174	66	0.061	50	0.018
Other CNS inflammation	5	60	0.415	40	0.690	0	0.708	60	0.174	20	0.690	20	0.827
Astrocytoma	4	25	0.690	0	0.415	0	0.708	50	0.685	50	0.061	25	0.827
Demyelinating lesions	4	25	0.690	0	0.415	0	0.708	50	0.685	0	0.690	25	0.827
PML	4	75	0.415	50	0.690	0	0.708	25	0.685	0	0.690	0	0.018
HIV encephalitis	2	100	0.415	50	0.061	0	0.708	50	0.685	0	0.690	50	0.827
Non-diagnostic	20	40	0.061	25	0.415	0	0.708	60	0.174	50	0.061	15	0.827

identified on MRI. The presence of an identifiable lesion on MRI was associated with an increase in the likelihood of having a diagnostic biopsy—38/51 diagnostic biopsies with a focal lesion compared to 4/11 when diffuse changes on MRI were present (Table 1).

Cerebrospinal fluid (CSF) analysis was performed on 58 patients (93.5%), while 14 (22%) patients underwent electroencephalographic studies. All patients with suspected vasculitis performed a diagnostic angiography.

Pleocytosis and inflammatory CSF changes were identified in 23 patients, although no further insight into the definitive diagnosis was achieved. Other routine laboratory findings, as well as microbiology studies, were also unhelpful in guiding diagnosis.

Biopsy method

The decision for the biopsy method was driven by the characteristics of the lesion. Identifiable lesions on MRI or contrast head CT underwent biopsy guided by neuronavigation (Medtronic StealthStation) or stereotaxy (Fischer ZD Stereotactic Head Frame or Leksell Stereotactic System), respectively.

Open biopsies were performed when diffuse changes were identifiable on MRI, with no circumscribed lesion, raising the suspicion for a heterogeneous brain disease, and aimed to sample meninges, cerebral cortex, and white matter. It was routinely performed in the right frontal lobe.

In our series, stereotaxy-guided biopsy was the method of choice, followed by open biopsy and neuronavigation-guided biopsy.

The diagnostic yield of stereotactic biopsy was 72.9%, similar to neuronavigation (72.72%). Open biopsies, as expected due to case selection, had a lower diagnostic rate (Table 1).

Brain biopsy was repeated in three cases, in which a targeting error was assumed.

Neuropathological diagnosis

Sixty-eight percent of the biopsies led to a definitive diagnosis (42 out of 62).

The most common histologic diagnosis was central nervous system lymphoma in eight patients. Astrocytoma, progressive multifocal leukoencephalopathy (PML), and demyelinating disease followed, with four cases each (Table 4).

The most common indications for biopsy were the suspicion of CNS inflammatory disease and CNS vasculitis, with 17 and 11 patients, respectively. Neuropathology confirmed the initial diagnosis in four cases of CNS inflammatory disease (23.5%) and in four cases of CNS vasculitis (36%).

Table 3 Summary of HIV patients' related biopsy

Age	HAART	Presentation	MRI	Diagnosis	Complications	Improvement
44	Yes	Focal signs	Focal lesion	Tuberculosis	No	Yes
40	Yes	Cognitive decline	Diffuse changes	No diagnosis	No	No
61	Yes	Seizures	Multifocal lesions	No diagnosis	No	No
63	No	Seizures	Multifocal lesions	HIV encephalopathy	No	Yes
35	Yes	Focal signs	Focal lesion	No diagnosis	No	No
26	No	Behavioral changes	Diffuse changes	No diagnosis	No	No
27	Yes	Focal signs	Focal lesion	PML	No	No
42	Yes	Focal signs	Multifocal lesions	HIV encephalopathy	No	No
42	No	Behavioral changes	Diffuse changes	PML	No	No
36	Yes	Focal signs	Focal lesion	Lymphoma	No	Yes
45	Yes	Cognitive decline	Multifocal lesions	Cryptococcosis	No	Yes

No initial clinical hypothesis of tumoral lesions was present in the eight patients diagnosed with lymphoma or the four patients diagnosed with astrocytoma.

The most common symptoms in the eight patients with lymphoma were cognitive decline and focal neurological signs (Table 2). Biochemical studies were within normal values, and CSF analysis revealed pleocytosis and increased protein level in three patients. Initial clinical diagnosis for these patients included vasculitis, CNS inflammatory disease, and infection.

Astrocytoma was diagnosed in three patients whose primary clinical suspicion was CNS inflammatory disease. Most commonly, patients diagnosed with astrocytoma presented with focal neurological signs and headache.

Four patients with ages ranging from 27 to 58 years old were diagnosed with PML. Two of these were HIV positive: one received immunosuppressive treatment for autoimmune disease and other chemotherapy. Three patients had an identifiable lesion, while only one presented diffuse changes upon MRI. Laboratory and CSF findings were unremarkable.

Uncommon diagnoses include Whipple's disease, mucormycosis, neurosarcoidosis, and CNS lesions secondary to rheumatoid arthritis and cystinosis. The list of neuropathological diagnoses is summarized in Table 4.

Whipple's disease was diagnosed in two patients. One was a 72-year-old female, who presented with a progressive cognitive decline, right hemiparesis, and gait disturbance. She underwent a stereotactic biopsy of a left frontal lesion, less than 2 weeks after symptomatic onset. The other case was a 68-year-old male presenting with over a month-long progressive dysphagia and dysarthria due to a brainstem enhancing lesion. Both patients started antibiotics upon diagnosis. Strikingly, treatment response was positive in the first patient, while only modest in the second case. These results support the importance of a prompt diagnosis and treatment in neuro-Whipple.

In one other case, a 35-year-old male presented with headache and cough. CSF studies showed increased proteins with low glucose levels, and no microorganism identified. Serum toxoplasmosis IgM was increased and IgG decreased, HIV was negative, as well as HBV and HCV. Brain MRI showed multiple lesions and thoracic CT showed a cavitary lesion. He was empirically treated for toxoplasmosis. Following clinical progression, with right hemiparesis and seizures, MRI showed

Table 4 Neuropathological diagnosis

Findings	Number of biopsies	%
Neuropathological diagnosis	42	68%
Lymphoma	8	19%
Astrocytoma	4	10%
Demyelinating lesions	4	10%
PML	4	10%
Cerebral amyloid angiopathy	2	5%
HIV encephalitis	2	5%
Infarct	2	5%
Tuberculosis	2	5%
Vasculitis	2	5%
Whipple's disease	2	5%
Histiocytosis	1	2%
Lesions secondary to cystinosis	1	2%
Lesions secondary to arthroid rheumatitis	1	2%
Mucormycosis	1	2%
Abscess	1	2%
Osteomyelitis	1	2%
Cryptococcosis	1	2%
Chronic meningitis	1	2%
Toxoplasmosis	1	2%
Neurosarcoidosis	1	2%
Non-diagnostic biopsies	20	32%

an increase in the size and number of lesions, and he underwent biopsy which was consistent with mucormycosis. Despite aggressive treatment following diagnosis, the patient died 2 months after biopsy.

Of the non-diagnostic biopsies, two showed normal parenchyma and 18 showed abnormal findings, including gliosis and non-specific inflammation. These patients with unknown diagnosis are a heterogeneous group. The most common symptoms included focal neurological signs (12) and headache (10), behavioral changes (8), and cognitive decline (5). CSF examination showed both pleocytosis and increased CSF protein in five patients, and increased CSF protein alone in one patient. Despite persistent studying, no definite diagnosis was achieved during a minimum follow-up of 3 years.

HIV patients

In our study, 11 HIV positive patients were included. One patient was diagnosed during CNS lesion investigation.

Presenting symptoms included paresis, visual deficit, seizures, cognitive decline, and behavioral changes.

Seven patients had identifiable lesions on MRI and underwent biopsy guided by stereotaxis (6) or neuronavigation (2). Open biopsy was the method used in three patients with diffuse changes on MRI.

The most common diagnoses in this group were PML and HIV encephalopathy. Seven out of 11 biopsies led to a diagnosis (63.6%). Based on biopsy findings, treatment modality was changed in five patients.

Outcome

Forty-two biopsies (68%) were diagnostic and the neuropathological result of the biopsy led to a change in clinical management in approximately 77.4% of the cases.

Importantly, in 10 patients, the initial clinical suspicion was confirmed, while 32 had a new and unexpected diagnosis. Thirty-two patients (50%) had a treatment specific for their diagnosis, of which 40% had a positive clinical response to the treatment initiated.

Post-biopsy complications happened in three patients (5%) and included seizures and abscess formation at the biopsy entry site in one HIV-positive patient.

Discussion

Brain biopsies have established utility in patients with CNS malignancies [8, 13]. Various authors have emphasized its benefit in immunodeficient patients with identifiable MRI lesions [3, 9, 22].

In individuals presenting with cognitive or neurologic decline of unknown etiology, its role remains controversial. Advances on brain imaging and CSF biochemistry can establish some guidance on clinical management and diagnosis; nevertheless, neuropathology still has a major role on definitive diagnosis [7, 18, 19, 21, 24].

We present a well-studied cohort of patients that underwent brain biopsy with a diagnostic yield of 68%.

Our results are within the wide range described in the literature, but actively contrast with the majority of studies which describe low diagnostic yields [4, 5, 11, 12, 21, 22]. Moreover, as previously observed by other authors, the higher diagnostic yields described in more recent series may be partly explained by the improvement in the diagnostic skills and surgical techniques [4, 21].

Importantly, all patients were rigorously investigated, with inconclusive results reached through all relevant non-invasive testing. Often, empirical treatment for most likely diagnosis had been initiated and only upon treatment failure was a biopsy indicated. Moreover, the majority of patients in our cohort had a targetable lesion on MRI and a tangible benefit from neuropathological diagnosis regarding treatment decision.

In our series, approximately one-third of the patients had biopsies for a primary clinical suspicion of inflammatory disease, while another third had multiple clinical suspicions and were labeled as unknown.

Inflammatory disease of the CNS, including demyelinating disease, is a heterogeneous group when considering clinical course, neuroradiological lesional features, and response to therapy.

Demyelinating disease diagnosis is established upon clinical, laboratory, CSF, and imaging criteria; however, the detection of standard histopathological criteria remains the conclusive confirmatory method and should be undertaken when clinical and paraclinical criteria cannot establish a diagnosis [14, 15]. Of the eight biopsies performed by clinical suspicion of atypical demyelinating disease, histopathological criteria for the diagnosis were met in three.

Vasculopathy was the clinical suspicion in 13 patients undergoing biopsy in our series, of which eight had undergone angiography with no findings suggestive of vasculitis. Of the patients submitted to biopsy, two were diagnosed with cerebral amyloid angiopathy and one with vasculitis after brain biopsy. Presentation included headache, cognitive impairment, and seizures. As symptoms tend to be non-specific and insidious, diagnosis may be delayed for months after symptom onset. One case of amyloid angiopathy is represented in Fig. 2.

Brain biopsy is the gold standard for vasculitis diagnosis and is known to have a low sensitivity, mostly due to the heterogeneous nature of the inflammation, leading to false-negative biopsies [17, 20]. This procedure becomes crucial

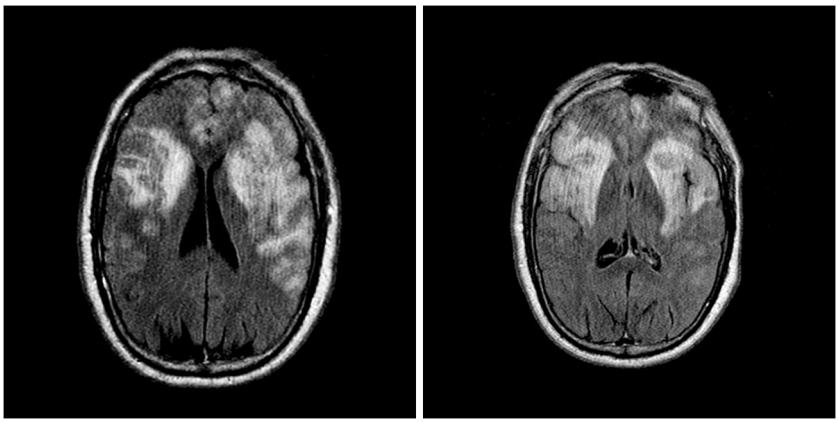

Fig. 2 A 76-year-old male presented with 2-week evolution of an encephalopathy-like syndrome. On MRI T1/FLAIR, he had multiple hyperintense lesions, bihemispheric. He was treated with methylprednisolone upon hospital admission, without improvement. After inconclusive non-invasive investigation, patient was referred for brain biopsy. Neuropathological exam concluded severe amyloid angiopathy

as differential diagnosis often includes diseases to which vasculitis treatment could be deleterious.

The revolution in HIV treatment with highly active antiviral drugs and the widespread use of prophylactic regimens has led to a decline in morbidity and mortality associated to this pathology and its attached opportunistic infections. Nevertheless, approximately 40 to 60% of AIDS patients present central nervous involvement, including infection, inflammatory diseases, and neoplasia [1, 2, 6]. Brain lesions are typically treated empirically according to current clinical guidelines, leaving brain biopsy to cases lacking improvement despite best medical treatment. Furthermore, imaging studies have become more accurate in the diagnosis decreasing the need for invasive diagnostic methods. Worldwide, the most common brain lesion in HIV patients is associated with *Toxoplasma gondii* infection [16]. The incidence of toxoplasma infection, together with CNS lymphoma, has dramatically decreased, while PML and HIV encephalopathies both have increased incidences in HIV patients [25].

In our study, 10 patients were positive for HIV infection. Of these, one was diagnosed during etiology investigation for the CNS lesion. The pre-operative imaging showed identifiable lesions on MRI in eight of these patients and an objective diagnosis was met in 70% of HIV patients. The decision to undergo brain biopsy in HIV patients was always taken upon treatment failure for the most likely cause of neurologic lesion or neurologic decline.

The presence of a defined lesion in the imaging studies, as well as HAART treatment and age, did not seem to influence the likelihood of a diagnostic biopsy. Based on biopsy findings, treatment modality was changed in five patients.

Sampling error was likely a major factor underlying non-diagnostic biopsies in a significant proportion of our subjects. Brain biopsy was repeated in three patients, all with identifiable lesions on MRI, and led to a definitive diagnosis. Venneti et al. showed increased sensitivity and specificity of diagnosis on sampling four brain regions, when compared to the frontal right cortex alone [23]. These results should be considered carefully when weighing the need and impact of a definitive diagnosis with the risks and potential catastrophic outcome of repeated brain biopsy. Moreover, it highlights the importance of autopsies, which cannot be overlooked despite current advances in diagnostic tools.

Patients with non-diagnostic biopsies had a minimum follow-up of 3 years, during which time no further insight into a diagnosis was unraveled.

Our institution is a tertiary referral center and possible selection bias may be present in this study. Most patients represent atypical clinical and imaging presentations or unusual diagnosis that could not be established through extensive diagnostic tests. Additionally, although all images were reviewed by an experienced neuroradiologist at our institution, due to the retrospective nature of our study, we cannot exclude whether pursuing other neuroimaging techniques would change clinical suspicion and avoid brain biopsy requirement. In the few cases with extensive neuro-imaging diagnosis, there was no further clue to the diagnosis and all required biopsy, indicating the need for a definite neuropathological diagnosis.

Our results validate a role for brain biopsies in the study and orientation of benign neurological disease. Heterogeneity of the patients within our cohort, concordantly to the series described by other authors, prevent us to generalize our results. They nevertheless reflect the suspected non-neoplastic cases considered for brain biopsy in a tertiary center.

We identify a crucial role for thorough clinical testing to actively identify patient that might benefit from brain biopsy, when such testing lacks a definite diagnosis. And our results support that clinical testing in the advent of a potential treatable disease must be time-conscious, in order to truly offer treatment benefit to the patient.

Our results are less affirmative in patients with diffuse changes or brain atrophy on MRI, in which brain biopsy has a low diagnostic yield. Further investigation is needed to identify markers of increased diagnostic yielding, improve surgical decision making and adapt biopsy technique to these patients.

Conclusions

In our series, a definitive neuropathological diagnosis was met in 42 patients (68%) and the most common diagnosis was CNS lymphoma, followed by PML, demyelinating disease, and astrocytoma. Of these, 32 patients (76%) had a specific treatment and 13 (40%) had a positive clinical response to the treatment initiated. Importantly, clinical management was changed in 48 (77.4%) patients following brain biopsy.

Our results suggest that brain biopsies should be considered in selective cases in which less invasive measures have been unable to reach a definitive diagnosis. Moreover, it should be considered while therapeutic intervention may still modify the course of disease.

Although being an invasive procedure, when carefully considered, our results support that it is a safe procedure (5% complication rate) and improves management of these patients.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

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