Impact of brain biopsy on management of nonneoplastic brain disease

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ABSTRACT

Introduction: Diagnostic yield of brain biopsy in neoplastic brain disease is high and its clinical impact is well established. In nonneoplastic brain disease with negative conventional investigation, decision to undergo invasive procedures is difficult due to its inherent risk and known lower diagnostic yield. Research question: What is the clinical impact of brain biopsy results on management of nonneoplastic brain disease?

Material and methods: A multidisciplinary team retrospectively reviewed and included all nonneoplastic brain disease cases submitted to biopsy between 2009 and 2019, in a tertiary hospital in Lisbon. Baseline characteristics were registered, including immunosuppression status, diagnostic workup, and treatment prior to biopsy. Diagnostic yield, clinical impact and in-hospital complication rates were assessed.

Results: Sixty-four patients were included, 20 (31.3%) of them immunosuppressed (15 HIV+ patients). Thirty-five (67.7%) were previously treated with steroids or antiinfectious agents, with higher percentage (93.3%) in the immunosuppressed group. Biopsy results were diagnostic in 46 (71.9%) cases. More frequent diagnosis was infectious in 20 (31.2%), neoplastic in 12 (18.8%) and inflammatory diseases in 8 (12.5%). Brain biopsy resulted on impact on patient’s clinical management in 56 (87.5%), of which 37 (57.8%) were submitted to treatment change. In-hospital complications were registered in 4 (6.6%) patients.

Discussion and conclusion: Brain biopsy had clinical impact, including a change in treatment, in most patients studied, and may be considered a useful diagnostic option in nonneoplastic brain disease. However, associated complication rate is not negligible, and previous thorough workup, patient selection and risk-benefit assessment are important.

1. Introduction

Brain biopsy (BB) has a critical role in the diagnosis of central nervous system (CNS) tumours (Livermore et al., 2014). However, its contribution in nonneoplastic CNS diseases (such as encephalitis, chronic meningitis and atypical space-occupying lesions) remains divisive.

In this set, studies have shown controversial results. In 2015, a meta-analysis showed low diagnostic success and clinical impact rates, although the initial hypothesis influenced these rates (Bai et al., 2015). However, recent small cohort studies (Noronha et al., 2019; Rice et al., 2011), showed higher rates, suggesting better patient selection. Also, in a 2016 meta-analysis including HIV + population with neurological disease, benefit of BB seemed to overcome risk (Lee et al., 2016), although most studies were pre-HAART (highly active antiretroviral therapy).

Recent evolution of imaging and laboratory testing may have increased diagnostic accuracy. Therefore, it is relevant to clarify whether brain biopsy is still a diagnostic tool to consider when facing nonneoplastic brain disease. The main goals of this study were to assess clinical impact and diagnostic success rates, and in-hospital complications of BB in patients with nonneoplastic brain disease, in which previous thorough
if electronic health records were insufficient, or if previous data (n = 1). Insufficient data (n = 5), and submission to previous BB (n = 1). Agreement about patient selection between neurologist and neurosurgeon was achieved in most cases (66; 84.6%).

Sixty-four patients were then included in the study. Five patients (7.8%) were treated with immunosuppressant drugs. Fifteen (23.4%) were HIV positive: 11 (73.3%) patients were treated with HAART at presentation and CD4+ lymphocyte count was <200 cells/μL in 7 (53.3%). In 3 patients, HIV diagnosis was made during workup. Patients were divided in two subgroups, regarding their HIV status. Baseline characteristics and previous management are displayed in Table 1.

Most patients (34; 53.1%) were studied in the neurology and neurosurgery departments. Thirteen (20.3%) patients were studied in other hospitals and then transferred to our centre for the procedure. Most procedures (42; 65.6%) were performed between 2009 and 2013.

Brain CT scan and MRI were performed in all patients, except in 2 who had an absolute contraindication for MRI. Lesions with mass effect were present in 34 (53.1%) patients. Lumbar puncture was performed in 42 (85.7%) patients; in 7 the presence of a space-occupying lesion contraindicated the procedure; in 15 data was not available. Two patients with suspected vasculitis were submitted to digital subtraction angiogram, and one to CT angiogram.

Data about previous treatment was available for 51 patients (11 HIV+). Most patients, including all HIV+, received empirical treatment. Most frequent treatments in non-HIV+ patients were steroids (23; 42.5%), followed by antibiotics (9; 22.5%). In HIV+ patients, antitoxoplasmosis (11; 72.7%) and anti-tuberculosis (5; 45.5%) treatments were the most frequent. In patients treated with steroids, the main goal was to treat brain lesion-related oedema.

3.2. Biopsy procedure

Time between first symptoms and BB was on average less than two months (Table 1). Median time between hospital admission for investigation and BB was significantly different depending on HIV status: 15.5 months (31.0 – 161.0) and 7 months (30.0 – 198.5) for HIV- and HIV+ patients, respectively. Anti-tuberculosis (3.3%) and antibiotic (5.9%) treatments were the most frequent in HIV+ patients. Anti-tuberculosis (n = 3; 7.5%) and anti-Mycobacterium (n = 1; 9.1%) were the most frequent in HIV- patients.

Table 1

| Baseline characteristics and management of patients before biopsy, according to their HIV status. |
|----------------------------------------------------------------------------------------------------------|
| HIV- population | HIV+ population | Total |
|-----------------|----------------|-------|
| Male patients (n, %) | 30 (61.2) | 10 (66.7) | 40 (62.5) |
| Age (mean, SD) | 54.3 (15.8) | 44.7 (7.7) | 52.0 (14.9) |
| Previous workup | | |
| Brain CT scan (n, %) | 49 (100.0) | 15 (100.0) | 64 (100.0) |
| Brain MRI (n, %) | 47 (95.9) | 15 (100.0) | 62 (96.9) |
| Lumbar puncture (n, %) | 30 (83.3) | 12 (92.3) | 42 (85.7) |
| Previous treatment | | |
| Steroids (n, %) | 17 (42.5) | 4 (36.4) | 21 (41.2) |
| Anti-tuberculosis (n, %) | 0 (0) | 8 (72.7) | 8 (15.7) |
| Anti-Mycobacterium (n, %) | 3 (7.5) | 5 (45.5) | 8 (15.7) |
| Antivirals (n, %) | 4 (10.0) | 1 (9.1) | 5 (9.8) |
| Antibiotics (n, %) | 9 (22.5) | 1 (9.1) | 10 (19.6) |
| Total (n, %) | 23 (57.5) | 11 (100.0) | 34 (66.7) |
| Timings (median, IQR) in days | | |
| Symptoms – biopsy time | 75.0 | 77.0 | 76.0 |
| (30.0–161.0) | (36.5–198.5) | (32.25–159.25) |
| Admission – biopsy time | 15.5 (4.0–35.5) | 38.0 | 23.0 (7.0–42.0) |
| (31.0–60.0) | | |

CT = computed tomography; MRI = magnetic resonance imaging; IQR = interquartile range; SD = standard deviation.
was open in 35 (53.1%) patients. In HIV patients, 3.3. Initial hypothesis
have vasculitis. (3; 4.7%), and anterior cerebral artery branch in one patient suspected to
meninges (11; 17.2%), meninges and brain cortex (3; 4.7%), brainstem, locations were brain hemispheres in 46 (71.9%) patients, followed by
open biopsy was more frequently performed (29; 59.2%). This difference was performed in 10 (66.7%) patients, while in HIV negative patients,
ment (including steroids), year of biopsy or type of procedure. Final
difference was found in diagnostic success rate, regarding previous treat-
was probable in
pachymeningitis. Non-infectious encephalitis (parenchymatous lesion of
unknown aetiology (meningeal gadolinium enhancement without
included multiple possibilities. In HIV negative patients, meningitis of
3.4. Diagnostic success
In 46 (71.9%) patients, brain biopsy led to diagnostic success (75.5% in
HIV negative patients and 60.0% in HIV positive patients). No dif-
fERENCE was found in diagnostic success rate, regarding previous treat-
ment (including steroids), year of biopsy or type of procedure. Final

Table 2
Main diagnostic hypothesis prior to brain biopsy, according to HIV status.

| Infectious disease (n, %) | HIV- population | HIV + population | Total |
|-------------------------|-----------------|-----------------|-------|
| - Unspecific brain abscess (n, %) | 12 (24.4) | 0 | 12 |
| - Progressive multifocal leukoencephalopathy (n, %) | 3 (6.1) | 2 (13.3) | 5 (7.8) |
| - Toxoplasmosis (n, %) | 0 | 4 (26.7) | 4 (6.3) |
| - Neurocysticercosis (n, %) | 1 (2.0) | 0 | 1 (1.6) |
| - Tuberculosis (n, %) | 1 (2.0) | 1 (6.7) | 2 (3.1) |
| - Multiple hypotheses (n, %) | 0 | 4 (26.7)* | 4 (6.3) |
| - Unspecific (n, %) | 1 (2.0) | 2 (13.3) | 3 (4.7) |
| Meningitis (n, %) | 11 (22.4) | 0 | 11 |
| - Pachymeningitis (n, %) | 7 (14.3) | 0 | 7 (10.9) |
| - Leptomeningitis (n, %) | 2 (4.1) | 0 | 2 (3.1) |
| - Pachyleptomeningitis (n, %) | 2 (4.1) | 0 | 2 (3.1) |
| Inflammatory disease (n, %) | 8 (16.3) | 0 | 8 |
| - Vasculitis (n, %) | 5 (10.2) | 0 | 5 (7.8) |
| - Multiple sclerosis (n, %) | 1 (2.0) | 0 | 1 (1.6) |
| - Unspecific (n, %) | 2 (4.1) | 0 | 2 (3.1) |
| Non-infectious encephalitis (n, %) | 5 (10.2) | 1 (6.7) | 6 (9.4) |
| Congophilic angiopathy (n, %) | 4 (8.2) | 0 | 4 (6.3) |
| Multiple hypotheses (n, %) | 3 (6.1)** | 1 (6.7)*** | 4 (6.3) |

Multiple hypotheses were considered equally: * tuberculosis vs toxoplasmosis (n = 2), toxoplasmosis vs PML (n = 1) and bacterial vs tuberculosis vs toxoplasmosis abscess (n = 1) ** amiloidoma vs infection, demyelinating vs vascular lesion, demyelinating vs vascular vs infectious disease. *** acute disseminated encephalomyelitis (ADEM) vs toxoplasmosis.

3.4. Clinical impact
In 56 (87.5%) patients, neuropathological diagnosis had clinical impact on management, and most patients (57.8%) benefitted from treatment change because of this result. Clinical impact rates in HIV negative and positive patients were 91.8% and 73.3% respectively (Table 4).

Diagnostic success and clinical impact rates according to initial hy-
pothesis and final diagnosis are displayed in Table 5. When final diag-
nosis confirmed the initial hypothesis, all diagnosis had clinical impact and 17 (65.4%) led to treatment change. When BB was nondiagnostic, 11 (61.1%) results still had a clinical impact, and 3 (16.7%) led to treatment change.

Table 3
Final neuropathological results according to HIV status.

| Final neuropathological diagnosis | HIV- population | HIV + population | Total |
|----------------------------------|-----------------|-----------------|-------|
| Infectious disease* (n, %) | 16 (32.7) | 4 (26.7) | 20 (31.2) |
| - Bacterial brain abscess | 11 | 1 | 12 |
| - Progressive multifocal leukoencephalopathy | 1* | 2* | 3 |
| - Tuberculosis | 2* | 0 | 2 |
| - Herpetic meningoencephalitis | 2* | 0 | 2 |
| - Toxoplasmosis | 0 | 1* | 1 |
| Neoplasm (n, %) | 7 (14.3) | 5 (33.3) | 12 |
| - Non-Hodgkin B cell Lymphoma | 2 | 3 | 5 |
| - Intravascular B cell Lymphoma | 2 | 0 | 2 |
| - Anaplastic astrocytoma | 1 | 1 | 2 |
| - Glioma | 1 | 0 | 1 |
| - Gliomatose cerebri | 0 | 1 | 1 |
| - Meningioma, grade I OMS | 0 | 1 | 1 |
| Inflammatory disease (n, %) | 8 (16.3) | 0 (0) | 8 (12.5) |
| - Hypertrophic pachymeningitis | 4 | 0 | 4 |
| - Vasculitis | 2 | 0 | 2 |
| - IgG4 disease | 1 | 0 | 1 |
| - Multiple sclerosis | 1 | 0 | 1 |
| Other | 6 (12.2) | 0 (0) | 6 (9.4) |
| - Congophilic angiopathy | 4 | 0 | 4 |
| - Meningitis | 2 | 0 | 2 |
| Non-diagnostic | 12 (24.5) | 6 (40.0) | 18 (28.1) |
75% in non-HIV patients, which was higher than most previous studies (Noronha et al., 2019; Rice et al., 2011). A 2015 meta-analysis including 831 immunocompetent patients disclosed a diagnostic success rate of 54% with great heterogeneity depending on the initial hypothesis (Bai et al., 2015). Primary angiitis of CNS and atypical dementia hypotheses were associated with higher rates (over 60%), while only 30% of chronic meningitis hypothesis had a definite diagnosis. However, only 3/20 studies included were published after 2010. Recently, there seems to be a better selection of cases using non-invasive methods and improved surgical techniques, which is supported by a strong correlation between diagnostic success rates and time interval of the studies (Bai et al., 2015; Noronha et al., 2019).

Other aspects may explain our high diagnostic rate. In our study, all cases had an imaging-defined target, which is known to be associated with higher diagnostic yield (Bai et al., 2015; Noronha et al., 2019; Rice et al., 2013; Wong et al., 2010). PCR techniques in brain tissue led to final diagnosis in 7 cases, and previous studies do not mention the use of this technique. Also, some selection bias may have occurred, as the initial hypothesis was confirmed in more than one third of cases. However, this is common in the literature: biopsy confirmed preoperative diagnosis in 46% of encephalitis cases (Abdullah et al., 2017); in nonneoplastic disease, neuropathology confirmed 15.6% of all cases, including 23.5% of CNS inflammatory disease and 36% of CNS vasculitis (Noronha et al., 2019).

4.2. Clinical impact

The clinical impact of all final diagnoses (including those of confirmation) is therefore essential. Overall, we found that over 80% of BB had clinical impact on patient management, and most led to treatment change. Reported clinical impact rates have been very heterogeneous, between 8 and 30%, depending on indication (Bai et al., 2015; Schuette et al., 2010). However, recent quoted studies show impact rates between 60 and 80%, like ours (Noronha et al., 2019; Rice et al., 2011). Higher diagnostic success rates will likely lead to higher clinical impact rates. Also, better disease knowledge and treatment advances in the last decade could explain this difference to former studies.

In our cohort, almost one fifth of our patients were diagnosed with brain neoplasm, even though primary hypothesis was nonneoplastic. More than 90% of definitive neoplasm diagnosis influenced treatment change. This phenomenon seems to be widespread. It has been showed that lymphoma and astrocytoma were among the most common histologic diagnosis when nonneoplastic brain disease was the initial hypothesis (Noronha et al., 2019), whereas the second most common diagnosis in chronic meningitis hypotheses was neoplasm (Bai et al., 2015). It is not unusual to have neoplasm in the list of differential diagnosis of atypical neurological conditions, even when it is not the primary hypothesis. Diagnosis of brain neoplasm has a great clinical impact and treatment may improve prognosis if diagnosis is made soon.

Table 4
Clinical impact of brain biopsy, according to HIV status.

| Clinical impact (n, %) | HIV negative | HIV positive | Total |
|-----------------------|--------------|--------------|-------|
| - Change of treatment | 30 (61.2)    | 7 (46.7)     | 37 (57.8) |
| - Other              | 13 (26.5)    | 4 (26.7)     | 17 (26.6) |

* Other: better orientation or prognostic acuity.

Table 5
Diagnostic success and clinical impact rates according to category of diagnostic hypotheses and final diagnoses.

| Diagnostic success | Clinical impact |
|--------------------|-----------------|
|                     | Total           | Changed treatment |
| **Initial hypothesis** |                 |                   |
| Infectious disease (n, %) | 24 (77.4) | 27 (87.1) | 19 (61.3) |
| Inflammatory disease (n, %) | 5 (62.5) | 8 (100.0) | 6 (75.0) |
| Meningitis (n, %) | 8 (72.7) | 10 (90.9) | 6 (54.5) |
| Encephalitis (n, %) | 3 (50.0) | 5 (83.3) | 2 (33.3) |
| Congophilic angiopathy (n, %) | 4 (100.0) | 4 (100.0) | 2 (50.0) |
| Multiple hypotheses (n, %) | 2 (50.0) | 2 (50.0) | 2 (50.0) |
| **Final diagnosis** |                 |                   |
| Infectious disease (n, %) | – | 20 | 15 (75.0) |
| Neoplastic disease (n, %) | – | 11 (91.7) | 11 (91.7) |
| Inflammatory disease (n, %) | – | 8 (100.0) | 6 (75.0) |
| Meningitis (n, %) | – | 2 (100.0) | 0 |
| Congophilic angiopathy (n, %) | – | 4 (100.0) | 2 (50.0) |
| Nondiagnostic (n, %) | – | 11 (61.1) | 3 (16.7) |

3.6. In-hospital follow-up

Information data about follow-up after biopsy was available in 60 patients (14 HIV-). In-hospital median stay after procedure was 12.0 (IQR 2.0–31.5) days. Seven patients had in-hospital occurrences between BB procedure and hospital discharge (Table 6). Four patients (66%) had procedure-related complications. One (7.1%) HIV+ patient had a complication after procedure, and three died during hospitalization, of not procedure-related causes. All cases of death occurred in patients with diagnostic biopsies. Procedure related mortality rate was zero.

4. Discussion

4.1. Diagnostic success

In over half of cases, brain biopsy led to diagnostic success, reaching 75% in non-HIV patients, which was higher than most previous studies (Bai et al., 2015; Josephson et al., 2007; Abdullah et al., 2017; Pulhorn et al., 2008; Schuette et al., 2010; Wong et al., 2010; Burns et al., 2009).

Table 6
Description of in-hospital occurrences after brain biopsy in seven patients.

| HIV status | Admission-biopsy time (days) | Main diagnostic hypothesis | Biopsy type | Final diagnosis | In-hospital occurrences | Time after BB (days) |
|------------|------------------------------|---------------------------|-------------|-----------------|------------------------|---------------------|
| Pos.       | 154                          | Infectious lesion         | S           | Anaplastic astrocytoma | Not procedure-related death | 2                   |
| Pos.       | 78                           | Toxoplasmosis             | S           | PML              | Not procedure-related death | 64                  |
| Pos.       | 35                           | Toxoplasmosis             | S           | Non-Hodgkin lymphoma | Not procedure-related death | 20                  |
| Pos.       | 46                           | PML                       | S           | Nondiagnostic    | Symptomatic parenchymatous haemorrhage | 1                   |
| Neg.       | 7                            | Brain abscess             | S           | Brain abscess    | De novo ventriculitis  | 1                   |
| Neg.       | 44                           | Vasculitis                | O           | Small-vessel vasculitis | Symptomatic subdural haematoma | 2                   |
| Neg.       | 14                           | Vasculitis                | S           | Nondiagnostic    | Symptomatic parenchymatous haemorrhage | 1                |

Pos. – positive; Neg. – negative; S – stereotactic; O – open; PML – progressive multifocal leukoencephalopathy; BB – brain biopsy.
enough, particularly in a young population as it was ours.

The clinical impact rates we present are higher than the diagnostic success rates. This is due to the fact that two thirds of nondiagnostic BB had clinical impact and 17% led to treatment change. Some information may redirect workup, exclude fewer probable conditions, allow withdrawal of useless treatments or simply better define prognosis, as others stated (Bai et al., 2015; Rice et al., 2011). On the other side of spectrum, not all definite diagnosis had significant clinical impact. Decision to submit a patient to such an invasive procedure should always have in mind its potential and clinical benefit, avoiding pure diagnostic ambitions.

4.4. In-hospital follow-up

During in-hospital follow-up, 4 (6.6%) patients had procedure-related complications. Procedure-related mortality was zero. This is in line with recent series where complication rates varied between 4% and 9% (Bai et al., 2015; Noronha et al., 2019; Rice et al., 2011; Pulhorn et al., 2008; Schuette et al., 2010; Wong et al., 2010; Gilkes et al., 2012). Most common complication in our cohort was symptomatic haemorrhage, as also shown in a recent meta-analysis (Bai et al., 2015), particularly in stereotactic procedures. Stereotactic biopsy is known to be associated with higher risk of parenchymatous haemorrhage (Livermore et al., 2014). These morbidity and mortality rates are lower than the ones associated to neoplastic disease biopsy (Livermore et al., 2014).

Although one might think HIV+ patients were more likely to have procedure-related complications, described morbidity and mortality rates for biopsy procedures in HIV + population are 5.7% and 0.92%, respectively (Lee et al., 2016). In our cohort, one HIV+ patient suffered a symptomatic parenchymatous haemorrhage after biopsy. During in-hospital follow-up, 3 HIV+ patients died of non-procedure-related causes. They were diagnosed with serious conditions (brain neoplasm and PML) and were in a very vulnerable condition during hospital stay. One of the patients was submitted to biopsy five months after admission. This suggests brain biopsy in HIV+ patients is equally safe, but timing of procedure may play a more important role to influence their prognosis.

4.5. Limitations

Being a retrospective study, it has limitations, particularly concerning missing data regarding previous workup and follow-up after procedure. Around 20% of patients were studied elsewhere and transferred to our centre temporarily for biopsy procedure, hampering data collection. Also, referral bias may have occurred towards the more challenging cases. Regarding neuropathological analysis, there was no minimal tissue sample volume required, and due to lack of collection of neuroimaging follow-up data, imaging was not reviewed by our team to confirm biopsy target accuracy. Although small, our cohort size is comparable to other studies in the same time length (Noronha et al., 2019; Rice et al., 2011; Acosta et al., 2018). Our HIV+ cohort is particularly small, but most of previous studies had wider inclusion criteria, such as neoplastic hypotheses. Finally, we cannot exclude some bias in patient inclusion and classification by the experts. Still, to minimize this, all cases were independently reviewed in a blinded process. We opted for a dichotomic decision (success: yes/no) to facilitate data analysis and interpretation. However, the degree of success also depends on the clinical course, previous workup and initial hypothesis considered and thus the expert decision on this outcome is ultimately subjective but reflects real-life clinical practice. Large prospective multicentric studies could add more information to help better select these patients.

5. Conclusion

Our study shows recent data about the usefulness of brain biopsy in nonneoplastic disease, including HIV+ population in post-HAART era. We reinforce the importance of extensive previous workup and empirical treatment, weighted against optimal timing for procedure, in order not to miss the therapeutic window. In selected cases, we show higher rates of diagnostic success and clinical impact, with few procedure-related complications.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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