Neurological diseases of unknown etiology: Brain-biopsy diagnostic yields and safety

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Neurological Diseases of Unknown Etiology: Brain-Biopsy Diagnostic Yields and Safety

Running title: Brain Biopsy For Diseases of Unknown Etiology

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HIGHLIGHTS

- In patients undergoing brain biopsy for neurological diseases of unknown etiology, we found high rates of specific histological (71.3%) and final diagnoses (83.1%), leading to therapeutic management change(s) for 75% of cases.
- Immunodepression was independently associated with specific histological diagnosis.
- Brain biopsy–related mortality occurred in 1.1% and permanent neurological morbidity in 0.6% of the patients.
- For highly selected patients with neurological diseases of unknown etiology, brain biopsy has a high diagnostic yield and low frequency of severe complications.

ABSTRACT

Background: For nonneoplastic neurological diseases, no recommendation exists regarding the place or appropriate timing of brain biopsy. The aim of this study was to evaluate the diagnostic yield and safety of brain biopsies from patients with neurological diseases of unknown etiology.

Methods: We performed a retrospective cohort study from January 1, 2008 to December 31, 2018. We analyzed 1847 brain-biopsied patients, including 178 biopsies indicated for neurological diseases of unknown etiology. Specific histological and final diagnosis rates, positive diagnosis-associated factors, complication rate and complication-associated factors were assessed.

Results: Specific histological diagnosis and final diagnosis rates were 71.3% and 83.1%, respectively, leading to therapeutic management change(s) for 75.3% of patients. Brain- biopsy–related mortality and permanent neurological morbidity occurred in 1.1% and 0.6% of the patients, respectively. The multivariable logistic-regression model retained (odds ratio [95% CI] only immunodepression (2.2 [1.1-4.7]; *P*=.04) as being independently associated with specific histological diagnosis, while supratentorial biopsy-targeted lesions (4.1 [1.1-15.2]; *P*=.04) were independently associated with a final diagnosis. Biopsies obtained from comatose patients were less contributive to the diagnosis (0.2 [0.05-0.7]; *P*=.01). Prebiopsy platelet count <100 G/L (28.5 [1.8-447]; *P*=.02), hydrocephalus (6.3 [1.2-15.3]; *P*=.02) and targeted lesions <1 cm (4.3 [1.2-15.3]; *P*=.03) were independently associated with brain biopsy-related complications.

Conclusion: For highly selected patients with neurological diseases of unknown etiology, brain biopsy has a high diagnostic yield and low frequency of severe complications. We advocate that this procedure be considered early in the diagnosis algorithm of these patients.

Keywords: brain lesion; cryptogenic neurological disease; diagnostic workup; neuropathology; neurosurgery.

DECLARATIONS

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INTRODUCTION

The contribution of brain biopsy is well-established for patients with suspected neoplastic lesions, for which its diagnostic yield approaches 95% [1,2]. For nonneoplastic neurological diseases, no recommendation exists regarding the place or appropriate timing of brain biopsy. Limited data support using brain biopsy to determine a diagnosis in human immunodeficiency virus (HIV)-positive patients with neurological symptoms [3,4], cerebral angiitis [5], Creutzfeldt–Jakob disease [6] or dementia [7]. For patients with neurological diseases of unknown etiology, brain biopsy is usually the investigational modality of last resort after exhaustive workups with less invasive tests, including imaging, cerebrospinal fluid analysis and electroencephalography, have failed to make a diagnosis. Because brain biopsy is an invasive procedure carrying a risk of severe complications, many physicians favor empirical treatments over taking the risk associated with biopsy to establish a diagnosis.

Considering the lack of evidence to guide the decision to biopsy for this challenging subgroup of patients, we conducted a retrospective monocenter study to investigate brain-biopsy diagnostic yield and safety in adults with neurological diseases of unknown etiology.

METHODS

Patients

We retrospectively reviewed the medical records and histology reports of all adults brain-biopsied at our tertiary medical center, between January 1, 2008 and December 31, 2018. Patients meeting the following conditions were included: 1) neurological disease of unknown etiology or atypical cerebral evolution of systemic and/or neurological underlying diseases; 2) negative comprehensive less-invasive diagnostic work-up including physical examination, laboratory tests, morphological examinations and extra-neurological histological findings; 3) indication for brain biopsy validated by a multidisciplinary team including neurologists, neurosurgeons, neurooncologists, neuroradiologists, neuropathologists, internists and nuclear medicine specialists; and 4) complete 6 months follow-up post biopsy or death before 6 months.

Patients were not considered for brain biopsy until a comprehensive less-invasive diagnostic work-up was fully performed and came back negative.

Patients who underwent brain biopsy for histological confirmation of an obvious primary or secondary cerebral neoplasm, or brain abscess were not included. Patients with incomplete data were excluded. For the 4 patients with repeat biopsies, only the first was included in the analysis.

Study Variables and Outcomes

Main outcome variables were: 1) obtaining a specific histological diagnosis, 2) making a final diagnosis, 3) brain-biopsy–related complications. Other variables included demographic characteristics, medical history, clinical manifestations, laboratory findings before brain biopsy, full less-invasive diagnostic work-up conducted for every patient and 6-month survival postbiopsy.

Histological results of brain biopsies were categorized into 3 groups: specific lesion, nonspecific lesion, normal brain. Obtaining a specific histological diagnosis was defined as brain-biopsy findings of a specific lesion sufficient by itself to make a diagnosis and to modify therapeutic management. The final diagnosis was reached by combining the brain-biopsy findings integrated with the patient's medical history and the results of the less-invasive diagnostic work-up. Brain biopsies containing specific lesion(s) were classified as contributory to the final diagnosis. Brain biopsies with nonspecific lesion(s) could nonetheless be classified as contributing to a final diagnosis. A multidisciplinary discussion among neurosurgeons, pathologists, neuroradiologists, neurologists and internists determined whether a brain biopsy with nonspecific lesion(s) contributed to a final diagnosis. During those discussions, participants systematically and comprehensively reviewed each patient's medical history, neurological and extra-neurological findings, less-invasive diagnostic work-up, brain-biopsy microbiology and histology results. The treating physician's main hypothetical diagnosis and treatment at the time of biopsy and changes made thereafter were noted. Two senior neuroradiologists analyzed all the imaging studies, including available 3.0 Tesla magnetic resonance imaging (MRI) (T1-weighted and T2-weighted, fluid-attenuated inversion-recovery [FLAIR], T1-weighted with gadolinium injection, gradient-echo T2*-weighted, and diffusion-weighted) sequences and multiparametric imaging data. Two senior neuropathologists examined all histological slides. During the multidisciplinary discussion, participants had to agree unanimously that the brain biopsy contributed to making the final diagnosis.

Brain-biopsy–related complications were defined as occurring during the month following the procedure. In the light of current literature on complications of diagnostic intracerebral procedures, we used a previously published graded severity scale with composite items including a prevailing surgical component [8,9]: grade 1: complication visible only on postoperative computed-tomography (CT) scan or transient event that did not require treatment; grade 2: transient complication that resolved completely but required treatment; grade 3: persistent neurological deficit >12 months postbiopsy; grade 4: biopsy-related death.

Surgical Procedures and Postoperative Management

A stereotactic biopsy technique was used for deep-seated lesions. The biopsies were taken under local anesthesia with all the patients placed in a Leksell-G stereotactic frame; 3-dimensional, spoiled, gradient-recalled, gadolinium-enhanced MRI and FLAIR sequences were obtained on a 1.5 Tesla MR scanner (Signa, General Electric, Boston, MA) after intravenous injection of gadolinium contrast material. An enhanced CT scan was rarely obtained instead of the MRI for technical reasons. Once these images were acquired, the trajectory and depth were planned according to the lesion to be targeted. Stereotactic coordinates were calculated with Framelink (Medtronic, Minneapolis, MN) software. The biopsy path was carefully chosen so as to avoid damaging critical superficial and deep veins and arteries. This route was simultaneously controlled millimeter-by-millimeter in the 3 spatial planes (3D view), and in the perpendicular and parallel oblique views of the needle trajectory. The entry site was shaved, and biopsy was obtained under standard aseptic surgical conditions without antibiotic prophylaxis. Patients were place in a semi-recumbent position and the stereotactic arc was used to determine the incision site. After making a stab incision, a 3-mm twist-drill hole was made at the previously calculated coordinates. An intracerebral biopsy needle was then introduced through the drill hole and advanced towards the target and 6–10 tissue samples, ~1 × 10 mm, at different depths surrounding and within the targeted lesion.

For cortical and/or meningeal lesions, biopsies were obtained via open craniotomy or a burr hole. We considered a gold standard diagnostic open biopsy to be 1 cm^3 of leptomeninges and cortex including grey and white matter. For MRI-negative patients, the biopsy was preferentially taken from the right middle frontal lobe gyrus, unless history, examination or imaging asymmetry suggested another location would provide a higher diagnostic yield.

The tissue samples collected were divided into several parts for neuropathological, bacteriological, parasitological and virological investigations. When the available tissue was deemed sufficient, smears were routinely prepared for urgent intraoperative neuropathological examination [10]. When the histological diagnosis could not be made based on tissue from one target, another target was selected. When the differential diagnosis included infection, tissue was set aside for microbiology studies. The management of samples in the pathology lab relied on the following process: (i) systematic freezing of one fragment to allow further molecular investigations looking for infectious agents or for mutations of neoplasms or for an abnormal clonality of lymphoid cells, (ii) short fixation before overnight paraffin embedding to allow urgent preliminary results in less than 30 hours, (iii) a first-line panel of technics adapted to the clinical context and to the examination of the

smear, (iv) preparation of unstained sections to spare the sample from iterative sessions of microtome cutting and to allow fast execution of a second-line panel. The first line panel included -in the absence of neoplasm on the smear- : (i) Gram, Grocott methenamine silver, Periodic Acid-Schiff/PAS, and Ziehl-Neelsen stains to detect infectious pathogens, (ii) Ki67, CD3, CD20, Iba1 immunolabelings to evaluate inflammation, potential lymphoproliferation and microglial activation, (iii) if immunocompromised patient, toxoplasma and virus JC immunolabelings. The second-line panel was adapted to the histological aspect of the standard staining and to results of the first-line panel: for example Epstein-Barr Virus hybridization in case of large lymphoid B cells, or luxol blue and double immunolabeling of myelin basic protein & neurofilament in case of potential demyelinating lesion.

Patients were monitored for at least 6 h in the recovery unit. Prior to transfer to the neurosurgery department, a postoperative CT scan was obtained to rule out immediate complications.

Statistical Analyses

Results expressed as number (%) were compared with χ^2 tests; continuous variables expressed as mean ± SD or median [interquartile range, IQR] were compared with Student's *t*-test or Wilcoxon's rank test. Patients' demographic, clinical and biological characteristics were tested in univariable analyses for association with obtaining a specific histological diagnosis, final diagnosis or the occurrence of any complication.

Thereafter, multiple logistic-regression analyses using backward, stepwise variable elimination were run (with the variable exit threshold set at $P > 0.10$). Factors achieving $P \leq 0.10$ in our univariable analyses and parameters previously reported to be strongly associated with diagnosis or complication(s) were entered into the multivariable model. All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the model. Model goodness-of-fit was assessed with the determination coefficient (R^2). $P < .05$ defined statistical significance. Analyses were computed with IBM SPSS Statistics v22.0 software (IBM Corp, Armonk, NY).

Standard Protocol Approvals, Registrations and Patient Consents

The database is registered with the *Commission Nationale de l'Informatique et des Libertés*. In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or

therapeutic strategies; however, patients were informed of their inclusion in the study. The manuscript was prepared in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

Data Availability Statement

Anonymized data will be shared on request from any qualified investigator.

RESULTS

Study Population

During the study period, 1847 patients underwent a brain biopsy; the 178 biopsied to investigate a neurological disease of unknown etiology were included in the study (**Figure 1**). The yearly number of brain biopsies and their indications for the 1847 patients are reported in **Supplemental Table 1**. The main reason for those latter biopsies was the histological confirmation of an obvious primary or secondary cerebral neoplasm (*n* = 1504, 90.4%).

The general characteristics of the 178 retained patients and their brain biopsies are presented in **Table 1**. The male-to-female ratio was 1.9 and the mean age on biopsy day was 47.1 ± 15.4 years. Their medical histories worth noting included immunocompromised status (42.7%), autoimmune diseases (14.6%), HIV (14.0%), hematological malignancies (10.1%), organ transplantations (7.3%) and solid-organ tumors (6.2%). One-third had been taking or were prescribed corticosteroids before the biopsy. Clinical manifestations included neurological deficit (74.9%), extra-neurological symptoms (32.2%), altered consciousness (30.3%), seizures (28.1%), fever (15.5%) and coma (11.4%). Elevated cerebrospinal fluid proteins and meningitis, respectively, were reported in 53.8% and 30.3% of patients with lumbar puncture. Most patients had multifocal (58.8%), bilateral (54.2%) or gadolinium-enhanced (57.4%) lesions. The biopsy-targeted lesion was predominantly supratentorial (93.2%), with largest diameter >1 cm (71.0%) and gadolinium-enhanced (58%). The most frequent biopsy technique was stereotaxic (69.5%), with MRI-guidance for 74.8%.

Diagnoses and Main Outcomes

Brain biopsies contained a specific lesion, nonspecific lesion or normal brain, respectively, for 127 (71.3%), 46 (25.8%) and 5 (2.8%) patients. Nonspecific lesions contributed to a final diagnosis for 21/46 (45.7%) patients. A final diagnosis could be made for 148 (83.1%) patients (Figure 1), most frequently: autoimmune or

inflammatory diseases (21.9%), infections (20.2%), hematological malignancies (19.6%), demyelinating disease (6.7%), metastasis (3.9%) and glioma (3.4%) (**Table 2**). Four patients had multiple diagnoses. Another biopsy was obtained from 4 (2.2%) patients and it contributed to the diagnosis for 4 of them. Brain-biopsy findings led to therapeutic management change(s) for 75.3% of the patients. The mean ± SD follow-up postbiopsy was 23.7 ± 28.8 months and 1-year survival was 75.8%.

Diagnostic Yield-Associated Factors

Comparisons between patients with specific and nonspecific histological lesion are reported in **Table 1**. Patients with specific lesions suffered significantly more frequently from immunocompromised status, fever, meningitis and elevated C-reactive protein levels. The logistic-regression model for multivariable analyses retained only immunocompromised status as being a significantly independent predictor of a specific histological lesion (**Table 3**). Comparisons between patients whose biopsies contributed or not to the final diagnosis are presented in **Supplemental Table 2.**

Univariable analyses (**Supplemental Table 3**) identified patients given a final diagnosis as having only more frequent supratentorial biopsy-targeted lesions (95.2% vs. 83.3%; $P = .02$). The logistic-regression model for multivariable analyses retained (odds ratio [95% confidence interval]) supratentorial biopsy-targeted lesion (4.1 [1.1 to 15.2]; $P = .04$) as independent predictors of a final diagnosis, while biopsies obtained from comatose patients were less contributive to the diagnosis (0.2 [0.05 to 0.7]; $P = .01$).

Complications and Factors Associated with Them

During the month following the biopsy, 22 (12.3%) patients developed grade-1, -2, -3 or -4 complications (**Supplemental Table 4**). Fifteen (68.2%) of those complications were grade-1 asymptomatic and diagnosed only on systematic postbiopsy imaging. Seventeen complications were postbiopsy hemorrhages, none of which required surgical hematoma evacuation. Two biopsies were fatal: 1 in the context of acute myeloid leukemia and persistent profound thrombopenia, and the other of multiple myeloma on mechanical ventilation and hemodialyzed.

Univariable analyses of complication-associated factors are reported in **Supplemental Table 5.**

The multivariable logistic-regression model (**Table 4**) retained prebiopsy platelet count <100 G/L, hydrocephalus and targeted lesions <1 cm as being independently associated with developing a brain biopsy-related complication, while a prebiopsy history of seizures or neurological deficit was significantly associated

with less postbiopsy complication.

DISCUSSION

For patients with neurological disease of unknown etiology, the place of brain biopsy remains controversial, because it is an invasive option that should only be considered when the global benefit surpasses the risk of inducing harm.

Previous series, mostly published in the 1990s and 2000s, included 14 to 64 patients brain biopsied for cryptogenic neurological disease [5,11–20]. Their reported diagnostic yields were relatively low, 29–68% [11,14,15,18,20–23], leading some authors to argue that it was too low and that the procedure was not contributory to patient management [12–15,24], while others emphasized brain-biopsy usefulness [5,16–20]. Since then, the numerous breakthroughs made in neurosurgery, pathology, immunology and microbiology have increased the diagnostic yield and improved the safety of the procedure. Our frequency of diagnoses made directly with brain biopsies during the last decade was higher for our series (71.3%) and was even better (83.1%) when nonspecific lesions were interpreted in light of the patient's medical history. Moreover, since 2016, metagenomic next-generation sequencing (NGS) of brain tissue has enabled diagnoses that cannot be made using routine microbiological testing [25]. These recently reported new techniques [26] pave the way to further improve in the diagnostic yield of these invasive procedures. Further studies will be needed to evaluate the need for brain biopsy and its diagnostic yield is the setting of new neuronal antibodies and NGS techniques. Lastly, although 16.9% of the biopsies were non-contributory for a final diagnosis, they indeed excluded neoplastic or infectious diseases, thereby enabling specific therapy (e.g., immunosuppressants ...) to be started, if needed.

We highlighted several new characteristics associated with obtaining a diagnosis. First, immunocompromised status was the sole factor associated with specific histological lesions. This subgroup's frequency and diversity of neurological diseases (opportunistic infections, inflammatory diseases and neoplasia) [4,27–29] render brain biopsies highly informative. Moreover, dual pathologies were found in 4/76 (5.2%) immunocompromised patients. Second, infratentorial biopsy-targeted lesions were less frequently associated with making a final diagnosis. Deep cerebellum and brain-stem lesions, which prevent efficiently obtaining biopsies, are indeed technically more complex [30,31]. Third, contrary to preconceived ideas, small or noncontrast-enhanced lesions were not associated with a low diagnosis rate. Last, biopsies taken from comatose patients were less likely to contribute to the final diagnosis. In these patients, the urgent need for diagnosis might

lead to retain wider indication of brain biopsy. Although, our results suggest that the benefit/risk ratio should be careful weighed for these patients.

Comparing the diagnostic yields in a context of diseases of unknown etiology, brain biopsy appears to be highly beneficial compared to those of other solid-organ biopsies. The diagnostic yields were all lower than herein: 40–59% for transbronchial lung biopsies for suspected sarcoidosis, with a complication rate of 12% [32,33]; slightly better at ~65% for percutaneous biopsies of benign lung nodules [34]; worse with only 18% definite diagnoses for endomyocardial biopsies, which impacted therapeutic management for 29% of the patients [35]; 30–50% for accessory salivary-gland biopsies for Löfgren's syndrome and other forms of sarcoidosis [36,37]; and 81% for punch skin biopsies from patients with suspected cutaneous sarcoidosis [38].

Pertinently, brain biopsy is an invasive procedure as its complications may be fatal. However, large series of brain biopsies obtained for brain tumor investigations showed that permanent neurological morbidity and mortality frequencies were low, ranging from 0 to 5.6% [39,40] and 0 to 4% [41,42], respectively. Herein, we also reported a low rate of severe (grade 3–4, 1.7%) complications in the setting of neurological diseases of unknown etiology. Likewise the frequencies of silent hemorrhagic complications in our series (7.9%) agreed with those previously reported (7–26%) [43,44].

Intriguingly, the main factor associated with complications in our study was low platelet counts on the days preceding biopsy, despite all patients having had >100 G/L platelets the day of biopsy. This finding underscores that, for thrombocytopenic patients, perioperative platelet transfusions do not prevent the risk of late biopsy-site bleeding. Based on those findings, we think that a platelet count >100 G/L should be maintained for at least 7 days postbiopsy [45,46]; however, we observed very late (21 days) hemorrhagic complications in patients with sustained profound thrombocytopenia. For thrombocytopenic, brain-biopsy candidates, the procedure's benefit/risk ratio must be thoroughly evaluated, especially when sustained thrombocytopenia is foreseeable.

Notably, small targeted lesions were more frequently associated with complications. Those outcomes can be explained by the limited number of possible trajectories to reach the target lesion. Notably, the topography of lesions was not associated with complications. Finally, preoperative hydrocephalus was associated with a higher rate of postoperative complications, suggesting that brain biopsy could exacerbate radiological findings and clinical symptoms related to hydrocephalus, probably through hemorrhagic and edema-inducing mechanisms. Ultimately, we would like to emphasize that the risk of severe complications of a brain biopsy should always be weighed against the risks borne by the natural evolution of an undiagnosed and untreated severe neurological disease (lymphoma, leukemia, infection, cancer, vasculitis…). In many cases, the latter is frequently more life-

threatening than the former, as supported by the 2 biopsy-attributable deaths during the year following biopsy vs. 42 because of disease-attributed deaths.

In the end, we suggest that several elements should be required to consider a brain biopsy in a patient with neurological disease of unknown etiology : 1) 3.0 Tesla brain MRI with spectroscopy and perfusion sequence, 2) negative comprehensive less-invasive laboratory and morphologic work-up including a total-body CT-scan, 3) negative pathological examination of extra-neurological lesions, if present, 4) brain lesion considered accessible by a trained neurosurgical team, 5) no bleeding disorders and the possibility of maintaining platelets over 100 G/L during the first 7 days after the biopsy, 6) validation of the brain biopsy indication during a multidisciplinary discussion. When these criteria are met cumulatively, we advocate that this procedure be considered early in the diagnosis algorithm of these patients.

Our study has limitations and strengths. First, it is retrospective, monocentric, observational design, but many patients with rare diseases undergoing a rather uncommon procedure were included. Second, our definition of "neurological disease of unknown etiology" may be controversial; however, all cases were analyzed retrospectively during retrospective multidisciplinary discussions to ascertain the diagnosis. Third, our institution being a tertiary referral center induces a selection bias, but also reflects the real-world picture of neurological diseases of unknown etiology. While some of the final diagnosis in this study can usually be achieve without a brain biopsy (tuberculosis, viral encephalitis, multiple sclerosis, ADEM…), many patients were referred to our institution because of a diagnostic dilemma that had not been solved with the comprehensive less-invasive work-up. Fourth, we could not obtain the median time from symptoms onset to brain biopsy. Indeed, some patients had a long medical history with many clinical symptoms while others had no specific neurological symptoms. Last, brain-biopsy safety and efficacy in our center relies on the experience of our neurosurgeons and neuropathologists, and those results may not be immediately reproducible in every center.

CONCLUSIONS

Our results suggest that, for highly selected patients with neurological diseases of unknown etiology, brain biopsy has a high diagnostic yield and low frequency of severe complications. We advocate that this procedure be considered early in the diagnosis algorithm of patients with neurological diseases of unknown etiology.

REFERENCES

[1] Livermore LJ, Ma R, Bojanic S, Pereira EAC. Yield and complications of frame-based and frameless stereotactic brain biopsy--the value of intra-operative histological analysis. Br J Neurosurg 2014;28:637–44. https://doi.org/10.3109/02688697.2014.887657.

[2] Hall WA. The safety and efficacy of stereotactic biopsy for intracranial lesions. Cancer 1998;82:1749–55.

[3] Hornef MW, Iten A, Maeder P, Villemure JG, Regli L. Brain biopsy in patients with acquired immunodeficiency syndrome: diagnostic value, clinical performance, and survival time. Arch Intern Med 1999;159:2590–6.

[4] Antinori A, Ammassari A, Luzzati R, Castagna A, Maserati R, Rizzardini G, et al. Role of brain biopsy in the management of focal brain lesions in HIV-infected patients. Gruppo Italiano Cooperativo AIDS & Tumori. Neurology 2000;54:993–7.

[5] Alrawi A, Trobe JD, Blaivas M, Musch DC. Brain biopsy in primary angiitis of the central nervous system. Neurology 1999;53:858–60.

[6] Heinemann U, Krasnianski A, Meissner B, Kallenberg K, Kretzschmar HA, Schulz-Schaeffer W, et al. Brain biopsy in patients with suspected Creutzfeldt-Jakob disease. J Neurosurg 2008;109:735–41. https://doi.org/10.3171/JNS/2008/109/10/0735.

[7] Warren JD, Schott JM, Fox NC, Thom M, Revesz T, Holton JL, et al. Brain biopsy in dementia. Brain 2005;128:2016–25. https://doi.org/10.1093/brain/awh543.

[8] Mathon B, Clemenceau S, Hasboun D, Habert M-O, Belaid H, Nguyen-Michel V-H, et al. Safety profile of intracranial electrode implantation for video-EEG recordings in drug-resistant focal epilepsy. J Neurol 2015;262:2699–712. https://doi.org/10.1007/s00415-015-7901-6.

[9] Mathon B, Navarro V, Bielle F, Nguyen-Michel V-H, Carpentier A, Baulac M, et al. Complications After Surgery for Mesial Temporal Lobe Epilepsy Associated with Hippocampal Sclerosis. World Neurosurg 2017;102:639-650.e2. https://doi.org/10.1016/j.wneu.2017.03.128.

[10] Mathon B, Amelot A, Mokhtari K, Bielle F. Increasing the diagnostic yield of stereotactic brain biopsy using intraoperative histological smear. Clin Neurol Neurosurg 2019;186:105544. https://doi.org/10.1016/j.clineuro.2019.105544.

[11] Josephson SA, Papanastassiou AM, Berger MS, Barbaro NM, McDermott MW, Hilton JF, et al. The diagnostic utility of brain biopsy procedures in patients with rapidly deteriorating neurological conditions or dementia. J Neurosurg 2007;106:72–5. https://doi.org/10.3171/jns.2007.106.1.72.

[12] Anderson NE, Willoughby EW, Synek BJ. Leptomeningeal and brain biopsy in chronic meningitis. Aust N Z J Med 1995;25:703–6.

[13] Duna GF, Calabrese LH. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. J Rheumatol 1995;22:662–7.

[14] Javedan SP, Tamargo RJ. Diagnostic yield of brain biopsy in neurodegenerative disorders. Neurosurgery 1997;41:823–8; discussion 828-830.

[15] Schuette AJ, Taub JS, Hadjipanayis CG, Olson JJ. Open biopsy in patients with acute progressive neurologic decline and absence of mass lesion. Neurology 2010;75:419–24. https://doi.org/10.1212/WNL.0b013e3181eb5889.

[16] Hulette CM, Earl NL, Crain BJ. Evaluation of cerebral biopsies for the diagnosis of dementia. Arch Neurol 1992;49:28–31.

[17] Cheng TM, O'Neill BP, Scheithauer BW, Piepgras DG. Chronic meningitis: the role of meningeal or cortical biopsy. Neurosurgery 1994;34:590–5; discussion 596.

[18] Burns JD, Cadigan RO, Russell JA. Evaluation of brain biopsy in the diagnosis of severe neurologic disease of unknown etiology. Clin Neurol Neurosurg 2009;111:235–9. https://doi.org/10.1016/j.clineuro.2008.10.003.

[19] Wong SH, Jenkinson MD, Faragher B, Thomas S, Crooks D, Solomon T. Brain biopsy in the management of neurology patients. Eur Neurol 2010;64:42–5. https://doi.org/10.1159/000315032.

[20] Rice CM, Gilkes CE, Teare E, Hardie RJ, Scolding NJ, Edwards RJ. Brain biopsy in cryptogenic neurological disease. Br J Neurosurg 2011;25:614–20. https://doi.org/10.3109/02688697.2010.551677.

[21] Bai HX, Zou Y, Lee AM, Lancaster E, Yang L. Diagnostic Value and Safety of Brain Biopsy in Patients With Cryptogenic Neurological Disease: A Systematic Review and Meta-analysis of 831 Cases. Neurosurgery 2015;77:283–95; discussion 295. https://doi.org/10.1227/NEU.0000000000000756.

[22] Magaki S, Gardner T, Khanlou N, Yong WH, Salamon N, Vinters HV. Brain biopsy in neurologic decline of unknown etiology. Hum Pathol 2015;46:499–506. https://doi.org/10.1016/j.humpath.2014.12.003.

[23] Noronha C, Figueiredo G, Pinheiro C, Carvalho E, Calheiros A, Pires MM, et al. Brain biopsy in suspected non-neoplastic neurological disease. Acta Neurochir (Wien) 2019;161:1139–47. https://doi.org/10.1007/s00701-019-03910-8.

[24] Abdullah KG, Li Y, Agarwal P, Nayak NR, Thawani JP, Balu R, et al. Long-term utility and complication profile of open craniotomy for biopsy in patients with idiopathic encephalitis. J Clin Neurosci 2017;37:69–72. https://doi.org/10.1016/j.jocn.2016.11.013.

[25] Seilhean D. Infections of the central nervous system: Neuropathology. Rev Neurol (Paris) 2019;175:431–5. https://doi.org/10.1016/j.neurol.2019.07.006.

[26] Wilson MR, Sample HA, Zorn KC, Arevalo S, Yu G, Neuhaus J, et al. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. N Engl J Med 2019;380:2327–40. https://doi.org/10.1056/NEJMoa1803396.

[27] Alesch F, Armbruster C, Budka H. Diagnostic value of stereotactic biopsy of cerebral lesions in patients with AIDS. Acta Neurochir (Wien) 1995;134:214–9.

[28] Clifford null. Focal Brain Lesions in People with HIV. Curr Treat Options Neurol 1999;1:167–72.

[29] Clifford null. Central Neurologic Complications of HIV Infection. Curr Infect Dis Rep 1999;1:187–91.

[30] Tobin WO, Meyer FB, Keegan BM. Diagnostic Yield and Safety of Cerebellar and Brainstem Parenchymal Biopsy. World Neurosurg 2015;84:1973–6. https://doi.org/10.1016/j.wneu.2015.08.062.

[31] Shad A, Green A, Bojanic S, Aziz T. Awake stereotactic biopsy of brain stem lesions: technique and results. Acta Neurochir (Wien) 2005;147:47–9; discussion 49-50. https://doi.org/10.1007/s00701-004-0420-3.

[32] Sehgal IS, Bal A, Dhooria S, Gupta N, Ram B, Aggarwal AN, et al. Predictors of Successful Yield of Transbronchial Lung Biopsy in Patients With Sarcoidosis. J Bronchology Interv Pulmonol 2018;25:31–6. https://doi.org/10.1097/LBR.0000000000000439.

[33] Akten HS, Kilic H, Celik B, Erbas G, Isikdogan Z, Turktas H, et al. Diagnostic Yield of Transbronchial Biopsy in Comparison to High Resolution Computerized Tomography in Sarcoidosis Cases. Asian Pac J Cancer Prev 2018;19:1029–33. https://doi.org/10.22034/APJCP.2018.19.4.1029.

[34] Portela de Oliveira E, Souza CA, Inacio JR, Abdelzarek M, Dennie C, Gupta A, et al. Imaging-guided Percutaneous Biopsy of Nodules ≤1 cm: Study of Diagnostic Performance and Risk Factors Associated With Biopsy Failure. J Thorac Imaging 2019. https://doi.org/10.1097/RTI.0000000000000427.

[35] Khan T, Selvakumar D, Trivedi S, Rao K, Harapoz M, Thiagalingam A, et al. The value of endomyocardial biopsy in diagnosis and guiding therapy. Pathology 2017;49:750–6. https://doi.org/10.1016/j.pathol.2017.08.004.

[36] Michon-Pasturel U, Hachulla E, Bloget F, Labalette P, Hatron PY, Devulder B, et al. [Role of biopsy of the accessory salivary glands in Löfgren's syndrome and other forms of sarcoidosis]. Rev Med Interne 1996;17:452–5.

[37] Szpirglas H, Giozza S, Agbo-Godeau S, Le Charpentier Y. [Biopsy of the accessory salivary glands. 5 years' experience]. Rev Stomatol Chir Maxillofac 1994;95:204–6.

[38] Yanardag H, Tetikkurt C, Bilir M, Demirci S, Iscimen A. Diagnosis of cutaneous sarcoidosis; clinical and the prognostic significance of skin lesions. Multidiscip Respir Med 2013;8:26. https://doi.org/10.1186/2049-6958-8-26.

[39] Kongkham PN, Knifed E, Tamber MS, Bernstein M. Complications in 622 cases of frame-based stereotactic biopsy, a decreasing procedure. Can J Neurol Sci 2008;35:79–84.

[40] Lara-Almunia M, Hernandez-Vicente J. Frame-based Stereotactic Biopsy: Description and Association of Anatomical, Radiologic, and Surgical Variables with Diagnostic Yield in a Series of 407 Cases. J Neurol Surg A Cent Eur Neurosurg 2019;80:149–61. https://doi.org/10.1055/s-0038-1676597.

[41] Malone H, Yang J, Hershman DL, Wright JD, Bruce JN, Neugut AI. Complications Following Stereotactic Needle Biopsy of Intracranial Tumors. World Neurosurgery 2015;84:1084–9. https://doi.org/10.1016/j.wneu.2015.05.025.

[42] Riche M, Amelot A, Peyre M, Capelle L, Carpentier A, Mathon B. Complications after frame-based stereotactic brain biopsy: a systematic review. Neurosurg Rev 2020. https://doi.org/10.1007/s10143-019-01234-w.

[43] Grossman R, Sadetzki S, Spiegelmann R, Ram Z. Haemorrhagic complications and the incidence of asymptomatic bleeding associated with stereotactic brain biopsies. Acta Neurochir (Wien) 2005;147:627–31; discussion 631. https://doi.org/10.1007/s00701-005-0495-5.

[44] Weise LM, Bruder M, Eibach S, Seifert V, Byhahn C, Marquardt G, et al. Efficacy and safety of local versus general anesthesia in stereotactic biopsies: a matched-pairs cohort study. J Neurosurg Anesthesiol 2013;25:148–53. https://doi.org/10.1097/ANA.0b013e318274ce41.

[45] Field M, Witham TF, Flickinger JC, Kondziolka D, Lunsford LD. Comprehensive assessment of hemorrhage risks and outcomes after stereotactic brain biopsy. J Neurosurg 2001;94:545–51. https://doi.org/10.3171/jns.2001.94.4.0545.

[46] Kreth FW, Muacevic A, Medele R, Bise K, Meyer T, Reulen HJ. The risk of haemorrhage after image guided stereotactic biopsy of intra-axial brain tumours--a prospective study. Acta Neurochir (Wien) 2001;143:539–45; discussion 545-546.

FIGURE LEGENDS

Figure 1. Flow-chart of patient inclusion in this study on brain-biopsy contribution to diagnosis.

Table 1. Patient and Biopsy Characteristics with Comparison According to Biopsy Specific Lesion Status

Characteristic	**All patients** ***n* = 178**	**Specific lesion** ***n* = 127**	**No specific lesion *n* = 51**	***P***
Males	117 (65.7)	88 (69.3)	29 (56.9)	0.1
Age on biopsy day, years	47.1±15.4	47.4±15.4	46.4±15.5	0.7
Medical history				
Immunocompromised	76 (42.7)	62 (48.8)	14 (27.5)	0.009
Cardiovascular	34 (19.1)	22 (17.3)	12 (23.5)	0.3
Autoimmune diseases	26 (14.6)	21 (16.5)	5 (9.8)	0.2
Human immunodeficiency virus	25 (14.0)	21 (16.5)	4 (7.8)	0.1
Hematological malignancies	18 (10.1)	13 (10.2)	5 (9.8)	0.9
Organ transplantation	13 (7.3)	12 (9.4)	1 (2)	0.08
Solid-organ tumor	11 (6.2)	6 (4.7)	5 (9.8)	0.2
Treatments before biopsy				
Corticosteroids	60/173 (34.7)	42/122 (34.4)	18 (35.3)	0.9
Antiplatelet therapy	21/174 (12.1)	15/123 (12.2)	6 (11.8)	0.9
Anticoagulant	6/174 (3.4)	3/123 (2.4)	3 (5.9)	0.3
Clinical findings before biopsy				
Neurological defect	131/175 (74.9)	92/124 (74.2)	39 (76.5)	0.7
Altered consciousness (GCS 8-14)	53/175 (30.3)	38/124 (30.6)	15 (29.3/4)	0.9
Coma (GCS 3-7)	27/174 (15.5)	12/124 (9.7)	8 (15.7)	0.3
Seizure	20/175 (11.4)	38 (29.9)	12 (23.5)	0.4
Extra-neurological symptoms	56/174 (32.2)	43/123 (35)	13 (25.5)	0.2
Fever	50 (28.1)	24/123 (19.5)	3 (5.9)	0.02
Laboratory findings before biopsy				
Meningitis	44/145 (30.3)	35/99 (35.4)	9/46 (19.6)	0.05
Elevated CSF proteins	78/145 (53.8)	57/99 (57.6)	21/46 (45.7)	0.2
White blood cell count, <3 G/L	6/163 (3.6)	4/119 (3.4)	2/50 (4)	0.9

Hemoglobin, <10 g/dL	35/168 (20.8)	28/119 (23.5)	7/49 (14.3)	0.2
Platelet count, G/L	250 [197-317]	244 [192-307]	274 [221-334]	0.04
<150 G/L	24/169 (14.2)	19/120 (15.8)	5/49 (10.2)	0.3
<100 G/L	2/168 (1.2)	5/120 (4.2)	1/49 (2.0)	0.5
C-Reactive protein, >10 mg/L	50/169 (29.6)	41/120 (34.2)	9/49 (18.4)	0.04
MRI findings before biopsy				
Multifocal lesions	104/177 (58.8)	74 (58.3)	30/50 (60)	0.8
Bilateral lesions	96/177 (54.2)	64 (50.4)	32/50 (64)	0.1
Hydrocephalus	16/176 (9.1)	11/126 (8.7)	5/50 (10)	0.8
Gadolinium enhancement	101/176 (57.4)	75/126 (59.5)	26/50 (52)	0.4
Meningeal involvement	27/176 (15.3)	19/126 (15.1)	8/50 (16)	0.9
Largest lesion diameter, mm	18.3 [10.9-28.7]	18.2 [10.6-28.3]	19.6 [11.1-30.2]	0.9
<10 mm	40/172 (23.3)	29/123 (23.6)	11/49 (22.4)	0.9
10-20 mm	53/172 (30.8)	39/123 (31.7)	14/49 (28.6)	0.7
>20 mm	79/172 (45.9)	55/123 (44.7)	24/49 (49)	0.6
Biopsy-targeted lesion characteristics				
Subcortical	72/176 (40.9)	52/126 (41.3)	20/50 (40)	0.9
Deep-brain	64/176 (36.4)	44/126 (34.9)	20/50 (40)	0.5
Cortical	29/176 (16.5)	21/126 (16.7)	8/50 (16)	0.9
Meningeal	9/176 (5.1)	8/126 (6.3)	1/50 (2)	0.2
Supratentorial	164/176 (93.2)	119/126 (94.4)	45/50 (90)	0.3
Size >1 cm	125/176 (71.0)	93/126 (73.8)	32/50 (64)	0.2
Gadolinium-enhanced	102/176 (58)	74/126 (58.7)	28/50 (56)	0.7
Biopsy technique				
Stereotaxic	123/177 (69.5)	88/126 (69.3/8)	35 (68.6)	0.9
MRI-guided	92/123 (74.8)	67/88 (76.1)	25/35 (71.4)	0.6

Abbreviations: CSF = cerebrospinal fluid; GCS = Glasgow coma score; MRI = magnetic resonance imaging.

Continuous variables, expressed as mean ± SD or median [interquartile range (IQR)], were compared with Student's *t*-test or Wilcoxon's rank test; categorical variables, expressed as *n* (%), were compared with χ^2 tests.

Table 2. Final Diagnoses for the 178 Patients Brain-Biopsied for Neurological Diseases of Unknown Etiology

Final Diagnosis	**Value**
Autoimmune or inflammatory diseases	**39 (21.9)**
Cerebral vasculitis	16
Sarcoidosis	9
Behçet's disease	5
Autoimmune encephalitis	2
Others*	7
Infectious diseases	**36 (20.2)**
Toxoplasmosis	9
Progressive multifocal leukoencephalopathy	8
Tuberculosis	7
Viral encephalitis	7
Parasitic/fungal diseases	4
Nocardiosis	1
Hematological malignancies	**35 (19.6)**
Lymphoma	13
EBV-induced lymphoproliferative disease	12
Histiocytosis	6
AL Amyloidosis[£]	2
Graft-vs.-host disease	1
Acute myeloid leukemia	1
Demyelinating disease	**12 (6.7)**
Multiple sclerosis	6
Acute disseminated encephalomyelitis	6

Metastasis	**7 (3.9)**
Glioma	**6 (3.4)**
Others[†]	**9 (5.1)**
Multiple diagnoses[‡]	**4 (2.2)**
None	**30 (16.9)**

Abbreviation: EBV = Epstein–Barr virus; AL, Amyloid Light. Results are expressed as *n* (%) or *n*.

* Immune reconstitution inflammatory syndrome, 2; and 1 each: inflammatory pseudotumor, CD8+ encephalitis, Rasmussen encephalitis, paraneoplastic encephalitis or neuromyelitis optica.

[£]Two Lambda Light Chain Amyloidosis.

[†]One each: mitochondrial cytopathy, Alzheimer's disease, mycosis fungoides, radionecrosis, methotrexate toxicity, craniospinal hypotension pachymeningitis, hemiplegic migraine, progressive cerebral ataxia or orthochromic leukodystrophia.

[‡] Progressive multifocal leukoencephalopathy and EBV-induced lymphoproliferative disease *n* = 2, and 1 each: toxoplasmosis and Immune reconstitution inflammatory syndrome or toxoplasmosis and EBV-induced lymphoproliferative disease.

Table 3. Univariable and Multivariable Logistic-Regression Model Analyses of Factors Associated with Brain Biopsy Containing a Specific Lesion

Variable	Univariable analysis			Multivariable analysis		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Male	1.7	0.8-3.3	0.1			
Medical history						
Immunocompromised	2.5	1.2-5.1	0.01	**2.2**	**1.1-4.7**	**0.04**
Human immunodeficiency virus	2.3	0.7-7.1	0.1			
Clinical findings before biopsy						
Fever	3.8	1.1-13.2	0.03			
C-Reactive protein >10 mg/L	2.3	1.1-5.2	0.04			
MRI findings before biopsy						
Bilateral lesions	0.6	0.3-1.1	0.1			
Biopsy-targeted lesion characteristic						
Size >1 cm	1.6	0.8-3.2	0.2			

Abbreviation: OR = odds ratio; MRI = magnetic resonance imaging.

The multiple logistic-regression model was run using backward-stepwise variable elimination (with the variable exit threshold set at $P > 0.10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the **model**. $P < 0.05$ defined statistical significance.

***Table 4*.** Univariable and Multivariable Logistic-Regression Model Analyses of Brain-Biopsy Complication-Associated Factors (grade 1–4).

Variable	**Univariable Analysis**			**Multivariable Analysis**		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age, years	1.0	0.9-1.1	0.1			
Clinical findings before biopsy						
Neurological defect	0.4	0.2-1.1	0.07	**0.2**	**0.06-0.9**	**0.04**
Seizure	0.2	0.05-0.9	0.049	**0.08**	**0.1-0.4**	**0.006**
Laboratory findings before biopsy						
Elevated CSF proteins	2.0	0.7-5.2	0.16			
White blood cell count < 3G/L	3.5	0.6-20.6	0.6			
Platelet count <100 G/L	16.0	2.7-93.6	0.002	**28.5**	**1.8-447**	**0.02**
MRI findings before biopsy						
Hydrocephalus	2.6	0.7-8.9	0.1	**6.3**	**1.3-30.4**	**0.022**
Largest lesion diameter, mm						
<10 mm	2.7	0.8-5.9	0.1	**4.3**	**1.2-15.3**	**0.03**
>10 mm	0.4	0.1-1.1	0.1			
>20 mm	0.4	0.1-1.2	0.1			
Targeted-lesion characteristic						
Size > 1 cm	0.4	0.18-1.1	0.08			

Abbreviation: OR = odds ratio; CI = confidence interval.

The multiple logistic-regression model was run using backward-stepwise variable elimination (with the variable exit threshold set at $P > 0.10$). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the **model**. $P < 0.05$ defined statistical significance.

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SUPPLEMENTAL DIGITAL CONTENT

Supplemental Table 1. Yearly numbers and indications of brain biopsies between 2008 and 2018

Supplemental Table 2. Patient and biopsy characteristics with comparison according to biopsy contribution to the final diagnosis

Supplemental Table 3. Univariable and multivariable logistic-regression model analyses of factors associated with brain biopsy contributing to the final diagnosis

Supplemental Table 4. Details of the 22 brain-biopsy complications according their grade

Supplemental Table 5. Univariable analysis of factors associated with a brain-biopsy–related complication