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# An Audit on the Use of Brain Biopsies for Non-neoplastic Brain Diseases

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**Abstract**

**Introduction:** In cases where a brain tumour is suspected, brain biopsies are the gold standard method for confirming the diagnosis. Brain biopsies are not frequently performed in non-neoplastic diseases as they tend to be regarded as an investigation of last resort. The role of brain biopsies, and their impact on subsequent clinical care, in non-neoplastic brain disorders is not well-defined.

**Methods:** This is a retrospective analysis of brain biopsies for non-neoplastic brain diseases performed at a single tertiary neuroscience centre over a ten-year period, from 2008 to 2018. Cases were identified from neuropathology reports. The charts were reviewed where pre-operative clinical information and investigation results were documented and post-biopsy clinical outcome as well as management changes were also recorded. Data analysis was performed using the frequencies tool and Fisher-exact test via SPSS software.

**Results:** Twenty cases were identified from pathology reports. 60% of biopsies (n = 12) were pathologically diagnostic. In those who had clinical management following biopsy recorded, clinical management was altered in 84% (n = 16) of patients. Of those with clinical outcome recorded: 62% (n = 8) had a documented clinical improvement; 15% (n = 2) returning to pre-disease baseline while 46% (n = 6) of patients improved without returning to pre-disease baseline. Complications occurred in 5% of patients (n = 1), a lower respiratory tract infection.

**Discussion:** In comparison with previous papers, the diagnostic yield of biopsies in this study is high. This could be attributable to extensive investigations, particularly neuroimaging resulting in targeted biopsies. Clinical improvements were seen in higher rates compared to previous research and complication rates were low.

**Conclusion:** This study shows that brain biopsies are useful in the investigation of non-neoplastic neurological disease and can have a high diagnostic yield. Clinical outcome was, for the majority, positive with a significant proportion of the patients improving. Complications were rare and did not have an adverse effect on patient outcomes. Our findings support the inclusion of brain biopsies as part of the diagnostic algorithm for non-neoplastic neurological conditions of unknown aetiology.

**Keywords:** brain; biopsy; diagnosis; non-neoplastic; diseases

## Introduction

The use of the brain biopsy in neurosurgical clinical practice is well established. Brain biopsies are currently regarded as the gold standard method for diagnosis in the cases of neoplastic brain diseases [1]. Histological characterization of tumours and molecular information are crucial for optimising management to target specific pathophysiological drivers. Brain biopsies in cases where neoplasm is not suspected are not commonly performed, with their role in diagnosis being less clear.

Obtaining an accurate diagnosis for neurological conditions can be difficult. Brain biopsies can play an important role, but they are generally regarded as an investigation of last resort, only being considered after other investigative modalities (computed topography (CT), magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG) etc.) have been exhausted.

Previous studies have shown the role brain biopsy's can have in non-neoplastic brain disease [2], whereby research suggests that diagnostic yield could be as high as 36% [3]. However, these studies have been limited by their small sample size. Complications due to the brain biopsy are generally uncommon but include haemorrhages, seizures and, rarely, death post-operatively (which was found in one study) [4]. Brain biopsies are reported to have an impact on patient management in up to 63% of cases [5], also including an indirect benefit reported of preventing potentially harmful and inappropriate treatments [6].

The aim of this study is to: evaluate the diagnostic yield and safety of brain biopsies for non-neoplastic brain diseases in a tertiary referral centre; to determine if any of the clinical variables, imaging and laboratory tests are associated with a greater likelihood of yielding a biopsy with diagnostic value; to analyse if biopsy results significantly altered management

and clinical outcome; and to establish the rate and nature of complications in our centre.

## Methods

This research was commenced following ethical approval from the Clinical Research Ethics Committee, University College Cork. General data protection regulations (GDPR) guidelines were adhered to throughout this research project. Cork University Hospital was selected for this research as it is the only tertiary neuroscience centre in the south of Ireland and is where all adult brain biopsies are carried out for the south (approximately one third) of the country.

### Case Identification

All brain biopsies performed in Cork University Hospital over a ten-year period between January 2008 and December 2018 were identified from neuropathology reports. Cases that had a known diagnosis prior to the biopsy of a neoplastic lesion, brain abscesses, or empyema as well as those with focal mass lesions were excluded from the study. In one patient who underwent two brain biopsies, only the second biopsy was included as the first biopsy was not on target. Following application, and approval, from the Cork University Hospital audit office, the clinical notes for each patient were accessed from the hospital medical records department.

### Data Collection

All cases were reviewed using a standard protocol. Clinical details, laboratory investigations, brain imaging, and brain biopsy findings were recorded. All neuropathology reports and radiological reports were completed by a consultant neuropathologist and radiologist respectively. Imaging or pathology slides were not re-reviewed for the purpose of this review. The management of the patient and disease progression over time were also reviewed.

From the neuropathology reports, the biopsy yield was categorised as diagnostic, suggestive or non-diagnostic/inconclusive. If the histological features were specific and diagnostic of a disease independently of other information, the biopsy was categorised as diagnostic. If the findings were abnormal, with limited specificity, but provided information that allowed for a more confident diagnosis to be made in the particular clinical scenario along with the imaging findings, then the biopsy was classed as 'suggestive'. If there was no information of clinical value from the biopsy, then this was regarded as non-diagnostic or inconclusive. The pathological findings from the diagnostic biopsies were documented and the date on which the brain biopsy took place was also recorded.

In order to establish the clinical details and baseline of each case, the patients' medical charts were analysed in a chronological order from the initial presentation until the most recent entry. The date of the initial presentation as well as the case demographics, consisting of the age at biopsy and gender, were documented. The major findings from the patients' presenting history and the clinical exam findings were documented. This consisted of the most prominent or impacting symptoms or signs. Where documented, findings from collateral histories were recorded to aid in establishing the patients' clinical baseline. Correspondence between clinicians and discharge summaries were evaluated to establish further relevant clinical information. Each presenting complaint and examination finding was then categorised numerically. The patients' clinical status post-biopsy was documented by analysing entries to the medical chart from the time of biopsy until the most recent entry. This was then compared with the clinical baseline that was established on presentation and categorised as: deteriorated within 12 months; deteriorated after 12 months; no change; improved but not returning to clinical baseline; or returned to clinical baseline.

The investigations section of each medical chart, clinician correspondence, and discharge summaries were in turn evaluated to establish investigations that were performed, and their results. A list of all serological investigations performed prior to biopsy, along with the results, and the laboratory normal ranges were documented. Basic serological investigations consisted of full blood count, urea and electrolytes, liver function tests, thyroid function tests, c-reactive protein, erythrocyte sedimentation rate, coagulation screen, and lipid profile. Additional serological investigations included, but were not limited to, extended viral screening (including herpes simplex virus and human immunodeficiency virus (HIV) screen), syphilis and Lyme disease, autoimmune antibody screen, and anti-neutrophil cytoplasmic antibody (ANCA) titre. Serological investigations were categorised as normal or abnormal based on the results of these investigations using the laboratory normal ranges provided. CSF analysis results were also documented and using the laboratory's ranges, were categorised as normal or abnormal. The neuroimaging studies performed in each case were recorded. The results from CT brain or MRI brain were first recorded and categorised as normal or abnormal. The specific findings from MRI brains were then recorded and categorised numerically according to the main abnormality noted. The medical notes documented during the time period when the brain biopsy was performed and the surgical notes were evaluated to establish if any complications occurred, as well as the outcomes from these complications. Cases were investigated in different manners by different clinicians and so resulted in variability in investigations and results, this factor was taken into account however was not investigated for impact on outcome.

Therapeutic regimens prior to the biopsy were documented using the clinical notes, discharge summaries, and correspondences between clinicians. The categories of medications used for these regimens were recorded. The discharge summaries and clinical notes following the brain biopsy were assessed to establish if changes to management

occurred and these changes were recorded according to the type of drug introduced or withdrawn.

Data Interpretation and Analysis

In order to carry out the statistical analysis, the categorised data was transferred and labelled on IMB SPSS v26 software. The frequencies tool was used to establish the median age and standard deviation at the time of brain biopsy, the male to female ratio, the frequency in which the biopsies were performed each year, the presenting complaints, the neuroimaging performed, the serological, neuroimaging, and CSF analysis results, the biopsy yield, the most common pathological findings, management changes and the clinical outcomes. Crosstabulation and the Fisher-exact test were used to assess if there were any associations between serological analysis results and biopsy yield, CSF results and biopsy yield, imaging results and biopsy yield, biopsy yield and change to management, pathological findings and change to management, biopsy yield and clinical outcome, and change to management and clinical outcome.

Data was stored on a password protected computer stored within the neuropathology department. All data collected was anonymised with no patient identifiers present. The data will be stored in keeping with local guidelines whereby it will be deleted after 10 years.

## Results

Between January 2008 and December 2018, a total of 20 brain biopsies were performed for the investigation of non-neoplastic brain diseases of unknown aetiology. The frequency for which brain biopsies were performed for non-neoplastic brain diseases increased from 2014 going from an average of 1.75 biopsies being performed per year before 2014 to 2.6 biopsies being done thereafter. At the time of biopsy, the patients ages ranged from 40 to 90, with a median age of 67.5 (standard deviation 13.4 years). The group comprised of 14 males and 6 females who underwent brain biopsies (male to female ratio of 2.3:1).

Biopsy Yield and Pathological Findings

The pathological findings from brain biopsies are listed in Table 1. Sixty percent of biopsies were diagnostic (n = 12) with the most common diagnosis being amyloid angiopathy (n = 5, 42%). Seven of the twenty (35%) biopsies had a suggestive result that required correlation with neuroimaging or ancillary investigations while one biopsy (5%) was entirely inconclusive. Statistical evaluation did not find a significant correlation between the pre-biopsy clinical findings or investigation results, and biopsy yield or pathological findings.

**Table 1.** Pathological findings

| ***Pathological diagnosis*** | ***No. of patients (% of total)*** |
|---|---|
| Amyloid angiopathy | 5 (42%) |
| Demyelinating disorder | 2 (17%) |
| Vasculopathy | 2 (17%) |
| Arteriolosclerosis | 1 (8%) |
| Meningoencephalitis | 1 (8%) |
| Fungal infection | 1 (8%) |

Presenting Complaint

The most common presenting complaints are listed in Table 2. Of the twenty patients who underwent brain biopsy, seventeen patients (85%) presented with a combination of symptoms. Sixteen of the twenty patients (80%) had their biopsy within 12 months of the initial presentation. The duration from disease onset to biopsy occurring for the remaining four patients varied, with two of these patients (50%) showing symptoms for five years prior to biopsy. It was observed that of the patients diagnosed with amyloid angiopathy (n=5), three presented with confusion (60%).

**Table 2.** Presenting symptoms of the 20 patients who underwent brain biopsy

| **Presenting complaint** | **No. of patients (% of total)** |
|---|---|
| Confusion | 7 (35%) |
| Weakness | 6 (30%) |
| Headache | 5 (25%) |
| Speech disturbance | 5 (25%) |
| Visual disturbance | 4 (20%) |
| Fatigue | 3 (15%) |
| Memory deficits | 3 (15%) |
| Paraesthesia & numbness | 2 (10%) |
| Behavioural disturbance | 2 (10%) |
| Recurrent falls | 2 (10%) |
| Nausea & vomiting | 2 (10%) |
| Cognitive decline | 2 (10%) |
| Hemiparesis | 1 (5%) |
| Hallucinations | 1 (5%) |
| Deteriorating balance | 1 (5%) |
| Ataxia | 1 (5%) |
| Vertigo | 1 (5%) |
| Collapse | 1 (5%) |

Serological Analysis

Nineteen of the twenty patients had blood results available for review. Basic serological investigations were carried out in all cases (n = 19) while additional serology tests were performed in thirteen out of nineteen patients (68%). Twelve out of the nineteen patients (63%) had normal blood results while the remaining seven patients had abnormal findings (37%) as determined by the normal laboratory ranges provided.

Lumbar puncture and CSF analysis was performed in thirteen out of the twenty patients (65%). CSF analysis included quantification of white cells, red cells, protein, and glucose levels as well as polymerase chain reaction (PCR) testing for infectious agents. Eleven of the thirteen (85%) had abnormal CSF results which included raised white blood cells, increased protein, oligoclonal banding, and raised immunoglobulin G (IgG).

Imaging Investigations

All patients underwent neuroimaging to different extents prior to the biopsy taking place. Fourteen out of twenty patients (70%) had a plain CT brain before biopsy, four patients (20%) had a CT angiogram, nineteen patients (95%) had an MRI brain, and thirteen patients (65%) had both a CT brain and MRI brain. Abnormal imaging results were seen in eleven of the twelve (92%) diagnostic brain biopsies. The most common abnormality on MRI was white matter changes, which was reported in seven of the nineteen patients (37%) while ischaemia was the second most common finding in four of the nineteen patients (21%). Other abnormalities recorded included cerebral atrophy, haemorrhage, and gliosis.

Management Changes

From medical records, management regimens following the biopsy were available in nineteen of the twenty patients (95%). Brain biopsy results triggered a change to management in sixteen patients (84%). Of those who had their management plans changed, these were categorised as: immunosuppressants introduced; antihypertensives introduced; antimicrobial introduced; antipsychotics introduced; statin introduced; or NMDA receptor antagonist introduced. A graphical representation of all changes to management can be seen in Figure 1. The correlation between biopsy result and management change was not statistically significant.

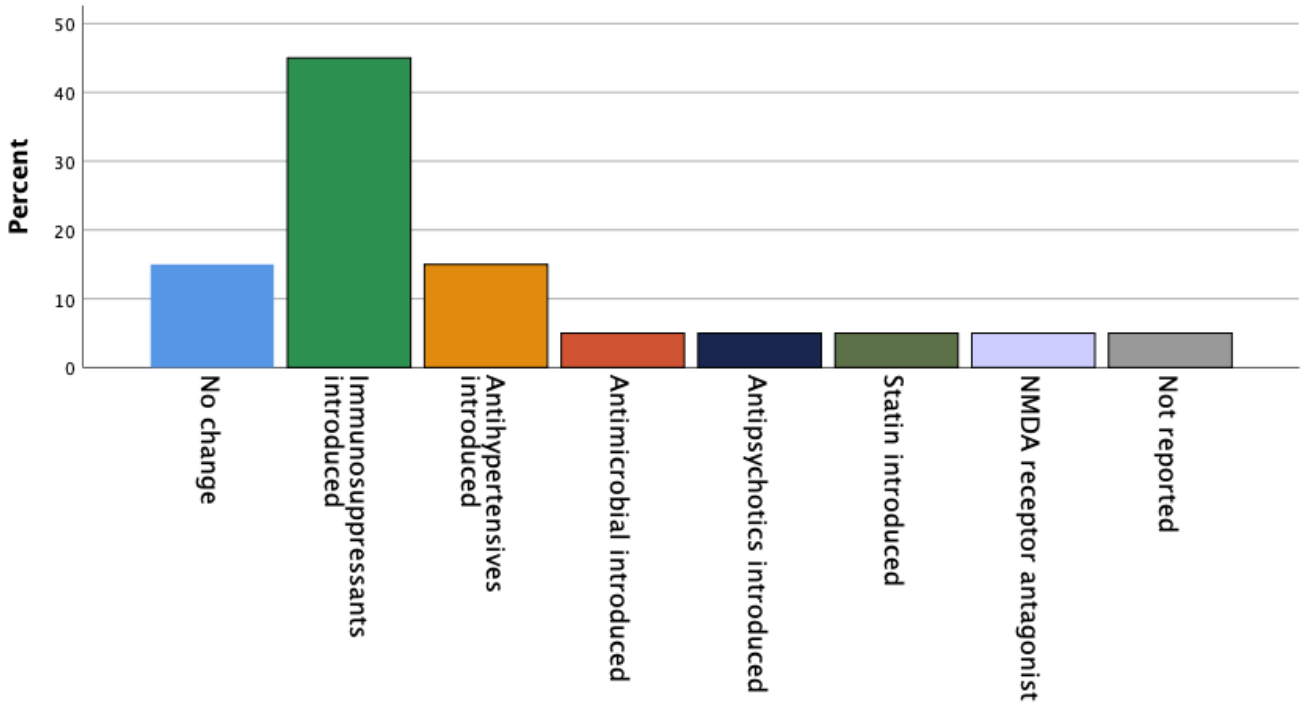


**Figure 1.** Management Change

Clinical Outcome

The clinical outcome was available by chart review in thirteen of the twenty patients. A graphical representation of the clinical outcome is available in Figure 2. Of the six patients (46%) who improved but didn't return to pre-disease clinical baseline, three (50%) had a diagnostic biopsy of vasculopathy, amyloid angiopathy, and arteriolosclerosis respectively, two (33%) had suggestive biopsy findings requiring correlation from other investigations, and one (17%) had inconclusive biopsy findings. The two patients (15%) who returned to their pre-disease clinical baseline were diagnosed with cerebral amyloid angiopathy. Of the patients who had a clinical improvement (n = 8, 62%), six (75%) had a change to management directly related to the biopsy findings while two patients improved despite no change to management (25%). Changes in these cases consisted of immunosuppressant introduction (n = 3, 38%), antihypertensives introduced (n = 2, 25%) and statin introduction (n = 1, 13%).

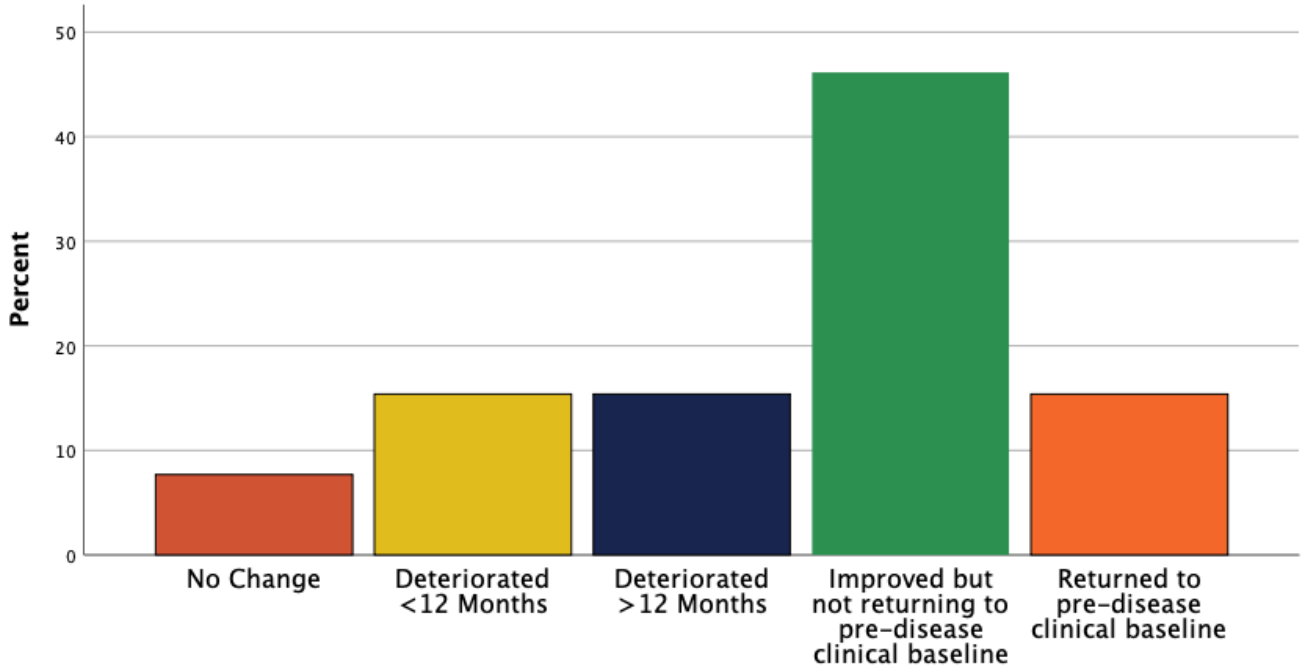


**Figure 2.** Clinical outcome

Complications

Post-operative complications were reported in one patient (5%). This complication, a hospital acquired lower respiratory tract infection, resolved with IV antibiotics and was not deemed to have had a detrimental impact on clinical outcome.

**Discussion**

In this study we showed that brain biopsies have a relatively high diagnostic yield – showing pathological features of a specific condition in 60% of cases. The findings from brain biopsies often lead to changes in patient management and subsequently improved clinical outcomes. The low complication rate associated with the procedure implies that brain biopsies are a reasonably safe investigative modality for non-neoplastic brain diseases.

Biopsy Yield and Pathological Findings

Previous research has shown that the diagnostic yield of brain biopsies for non-neoplastic brain diseases varies [2-13]. A relatively high diagnostic yield, as seen in this study, is not uncommon. It can be seen in these papers that a higher diagnostic yield is seen in research that has been conducted in recent years. Advances in imaging technology and improved surgical techniques may be contributary to this rise. It has been recognised that biopsy yield is higher in patients who have targeted brain biopsies following thorough neuroimaging, compared to those who did not [2,3]. The surgical technique used in performing the brain biopsies was not included in this study however it is has been reported that surgical technique does impact the diagnostic yield of brain biopsies [6].

In the context of available published research, the diagnostic yield in this study is quite high [2-4,6,7,9,13], while additional suggestive biopsy yields are comparable, ranging from 18% [6], to 42% [9]. Some studies, however, show a rate of inconclusive biopsies to be as high as 36% [5]. In general, this is likely to reflect the complex nature of many pathological processes, which do not affect all parts of the brain uniformly but rather have variable anatomical distributions. In general, medical brain biopsies are taken from the non-dominant frontal cortex so that the absence of pathology may reflect a sampling error rather than a true absence of intracerebral disease [14]. The high diagnostic yield of these brain biopsies shows that this investigative procedure should be considered as relatively effective and useful, especially if there is an atypical presentation or following inconclusive results of less invasive investigations.

Amongst the diagnostic biopsies, the most common pathology was cerebral amyloid angiopathy (CAA). CAA is characterized by the deposition of amyloid protein in the walls of cerebral and leptomeningeal vessels and can occur in isolation, or as part of Alzheimer's disease. The disease may be associated with mutations in the APP, presenilin 1 or presenilin 2 genes [15,16]. Although brain biopsy is the only way to definitively diagnose CAA [17], this is not commonly performed. The diagnosis generally relies on a typical clinical presentation with neuroimaging appearances that are regarded as strongly suggestive, such as multiple lobar haemorrhages [18,19]. Newer modalities, in particular

amyloid-PET CT imaging, as well as biochemical assays of CSF are also useful, although not universally available [20,21]. Amyloid PET or CSF amyloid testing were not performed in any of the five cases of CAA seen in our study. The advent of these newer diagnostic modalities may reduce the need to pursue diagnostic biopsies in the future.

According to The Modified Boston Criteria for diagnosing CAA [22], the presence of pathological tissue along with clinical data allows more definitive diagnosis to be made, where it can be titled 'probable CAA with supporting pathology'. In patients who have an atypical presentation of CAA, or are treatment resistant, this would allow a more definitive diagnosis to be made and tailored treatment commenced.

Management Changes & Clinical Outcome

Change in patient management was a central aspect of this audit. Comparison of patient management pre- and post-biopsy revealed 80% of those with recorded management following biopsy had changes made to their regimens. Furthermore, the introduction of immunosuppressants, steroids or second line immunosuppressants was the most common change made. Follow-up management was not studied in many published papers [5,9,11,13]. Recorded changes to management in existing literature ranges from 11% [9] to 80% [5] of patients having changes made following the outcome of brain biopsy. In these papers, the most common changes included the introduction of immune modulators [9,11,13], namely steroids. Steroids are among the most commonly prescribed drugs in neurology and there are a number of reasons for this [23]. From both clinical experience and published research [24], steroids have been proven to be an effective treatment option in a wide array of neurological conditions. Secondly, steroids rarely cause a deterioration or worsening of neurological conditions [23], despite the fact that the side effect profile for corticosteroids is extensive [25].

Within the context of previous research, our finding of improvement in clinical outcome in 61% of cases is somewhat higher than generally reported from the findings of previous studies (where clinical improvements following brain biopsy ranged from 26% [11] to 36% [3] of patients). In atypical presentations of conditions, definitive diagnosis from pathological analysis enables targeted and effective therapies to be implemented, in the hope of leading to disease regression and clinical improvement. The secondary benefit of pathological diagnosis is the ruling out of other pathological processes. This prevents the patient from being exposed to unnecessary and potentially harmful treatment regimens, such as the adverse effects of corticosteroids [6,25].

Complications

The safety of any diagnostic modality needs to be considered when implementing its use. Complications in relation to brain biopsies were looked for in all cases in this study. Only one patient (5%) experienced a complication, a lower respiratory tract infection. In comparison to other studies, where complications were seen in up to 16% [6] of cases, the complication rate in this study is low. Other complications included intracerebral haemorrhage, abscess or seizures [2,4,6,12]. Low complication rates and significant impacts on the patients clinical status suggest that this procedure is reasonably safe when appropriately targeted in investigating non-neoplastic brain diseases.

There are a number of limitations to this audit. The sample size of just twenty is small (although comparable to other studies [3,8] and data collection and analysis were conducted by a single person. This audit was also limited by its retrospective nature whereby there was some inconsistency in clinical documentation of patients' baseline clinical status, pre-biopsy investigations, biopsy techniques, management changes and importantly, follow-up outcome. Many of the patients that underwent a biopsy in this tertiary centre were referred from peripheral hospitals and so clinical outcome following biopsy was not documented. A re-evaluation of the use on brain biopsies for non-neoplastic brain diseases should be performed to assess if earlier implementation of biopsy impacts clinical outcome. If future studies were to be complete a larger sample size should be used, surgical techniques should be assessed, and a prospective study would enable for consistent data from all cases to be included with more details surrounding baseline clinical status, management regimens and clinical outcome. Re-audit using this study as a template should subsequently be undertaken.

The position of the brain biopsy in the diagnostic algorithm for non-neoplastic brain diseases is variable and is determined on a case-by-case scenario. Despite the high diagnostic yield from brain biopsies, the consensus still remains to pursue all other investigative options prior to brain biopsy. However it is important to ensure that it is not too late in the disease process, past any optimal treatment stage. This is difficult to establish as the rate of disease progression and its reactivity to treatment are difficult to accurately establish. Therefore a multi-disciplinary approach must be emphasised in considering brain biopsies. This involves neurologists, neurosurgeons and neuropathologists to carefully discuss each case, establish the differential diagnosis as well as the potential risks and benefits and to determine the optimal site of biopsy to maximise potential yield and minimise risk of neurological injury.

## Conclusion

In conclusion, we show that brain biopsies can have a significant role in the diagnostic algorithm for non-neoplastic brain diseases. It is particularly useful for atypical disease presentations where neuroimaging and serological investigations do not reveal a clear diagnosis. This review suggests that biopsies should be viewed as a more reliable mode of investigation in non-neoplastic brain diseases and are a reasonably safe procedure, with few complications, and

significant benefits. This should be determined on a case to case basis where the benefits of the biopsy outweigh the risks and we emphasise the importance of a multidisciplinary approach.

**List of Abbreviations Used**
ANCA: anti-neutrophil cytoplasmic antibody
CAA: cerebral amyloid angiopathy
CSF: cerebrospinal fluid.
CT: computed topography
EEG: electroencephalogram
GDPR: general data protection regulations
HIV: human immunodeficiency virus
MRI: magnetic resonance imaging
PCR: polymerase chain reaction
NMDA: N-methyl D-aspartate

**Conflicts of Interest**
The authors declare that they have no conflict of interests.

**Ethics Approval and/or Participant Consent**
This research was commenced following ethical approval from the Clinical Research Ethics Committee, University College Cork.

**Authors' Contributions**
DOF: made contributions to the design of the study, collected and analysed data and drafted the manuscript.
NB: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

**Acknowledgements**
I would like to thank Dr Antoinette O'Connor for her suggestions in completing this research and Dr Colm O'Tuathaigh for teaching and assisting in the completion of this study. Tables included in this paper were created using Microsoft Word. Figures included in this paper were created using SPSS Statistical Software.

**Funding**
This study was not funded.

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**Article Information**
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Fahed Abu-Hijleh, Foram Vyas, Vanessa Susevski
Article Dates: Received Feb 15 21; Accepted Aug 10 21; Published Oct 01 21

**Citation**
Please cite this article as follows:
O'Flynn D, Bermingham N. An audit on the use of brain biopsies for non-neoplastic brain diseases. URNCST Journal. 2021 Oct 01: 5(10). https://urncst.com/index.php/urncst/article/view/249
DOI Link: https://doi.org/10.26685/urncst.249