The utility of brain biopsy in paediatric cryptogenic neurological disease

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Abstract

Purpose
To characterise a single-centre experience of brain biopsy in paediatric cryptogenic neurological disease.

Method
Retrospective review of consecutive brain biopsies at a tertiary paediatric neurosciences unit between 1997-2017. Children <18 years undergoing biopsy for neurological pathology were included. Those with presumed neoplasms, and biopsy performed in the context of epilepsy surgery were excluded.

Results
Forty-nine biopsies, from 47 patients (25F, mean age±S.D. was 9.0±5.3), were performed during the study period. The most common presenting symptoms were focal neurological deficit (28.6%) and focal seizure (26.5%). Histopathological, microbiological and genetic analysis of biopsy material was contributory to diagnosis in 34 cases (69.4%). Children presenting with focal seizures, or with diffuse (>3 lesions) brain involvement on MRI, were more likely to yield a diagnosis at biopsy (OR 3.07 and 2.4, respectively). 12 patients were immunocompromised, and were more likely to yield a diagnosis at biopsy (OR 6.7). Surgery was accompanied by severe complications in 1 patient. The most common final diagnoses were infective (16/49, 32.7%), followed by chronic inflammatory processes (10/49, 20.4%) and occult neoplastic disease (9/49, 18.4%) were also common. In 38 cases (77.6%), biopsy was felt to have altered clinical management.

Conclusion
Brain biopsy for cryptogenic neurological disease in children was contributory to diagnosis in 69.4% of cases, and changed clinical management in 77.6%. Biopsy most commonly revealed underlying infective processes, chronic inflammatory changes, or occult neoplastic disease. Although generally safe, the risk of severe complications may be higher in immunocompromised and myelosuppressed children.
Introduction

The utility of brain biopsy for suspected brain tumours is well established and has a high diagnostic yield. Less well understood is the role of brain biopsy in cryptogenic neurological disease, which is defined by presentation with a severe neurological syndrome, in an acute or chronic fashion, whose aetiology remains unclear despite extensive investigation. The literature detailing the indications, diagnostic yield and morbidity of biopsy in children is sparse. Consequently, centres differ in opinion regarding the risk and value of the procedure. In addition, the increasing use of immunosuppression in children, mostly related to transplantation and inflammatory disease, has altered the spectrum of cryptogenic brain lesions. In the modern diagnostic era, with improved sensitivity of radiological, serological and genetic investigations, a limited number of paediatric series have been published. Prior publications relate to experience before 1980, when diagnostic pathways and imaging protocols, before the availability of magnetic resonance imaging (MRI), were very different. Other publications relate to adult practice, where a substantial proportion of biopsies are undertaken in the setting of neurodegenerative disease.

In the paediatric population, many common diagnoses such as vasculitis, infection and inflammatory disease, can be very effectively treated with modern pharmaceutical agents. Thus, diagnostic brain biopsy has the potential for high clinical impact in children.

The objective of this retrospective series of consecutive cases, derived from a quaternary institution with a high volume of paediatric transplant activity, is to describe our experience of brain biopsy for paediatric cryptogenic neurological disease with a focus on surgical technique, diagnostic yield and effect on patient management.

Methods

Patients were identified from a prospectively maintained neurosurgical operative database, which was retrospectively queried with the keyword “biopsy”, and subsequently filtered to exclude non-brain biopsies. This identified all brain biopsies carried out between 1997 and 2017. All patients were under the age of 18. Those undergoing targeted biopsy for suspected tumour, or biopsy performed in the context of resective epilepsy surgery, were excluded. Those included were all patients undergoing diagnostic biopsy for neurological presentations of uncertain aetiology. Our institution does not require additional patient consent or ethical approval for retrospective case note reviews of this nature.

Two paediatric neurologists (JH and CH) reviewed the case notes to assess the diagnostic workup and to confirm the cryptogenic nature of the neurological presentation. Pre-operative MRI and surgical techniques were reviewed by three neurosurgeons (SMT, PG and KA). MRI changes were characterised as diffuse (i.e. > 3 lesions visible), multifocal (2-3 lesions visible) or focal (single lesion visible). MRI changes were categorised as concordant with with final diagnosis when the radiologists’ report stated a single specific diagnosis which matched that from laboratory analysis of biopsy material. Adverse events were recorded prospectively in an operative database, and reviewed contemporaneously at departmental surgical morbidity and mortality meetings. Although there was no pre-determined panel of tests for each biopsy sample, the diagnostic considerations and requirements for each case were always discussed in advance with the pathologists and
microbiologists. All biopsy samples were sent ‘fresh’ from the operating theatre, and divided to allow processing for microbiology, including Gram stain, cultures and polymerase chain reaction (PCR) for the detection of nucleic acids, virology, electron microscopy and conventional pathology, including immunostaining. Histopathology was contemporaneously reviewed by two histopathologists (TSJ and BH). Biopsy samples were retrospectively categorised as diagnostic or not on the basis of the histopathological report and microbiological and virological studies. Biopsies with clear diagnostic descriptions on these grounds, and those with highly suggestive changes (such as chronic or granulomatous inflammation), or where an infectious agent was newly identified, were classified as being contributory to diagnosis.

Descriptive statistics were performed in R (R Core Team 2017). Fisher’s exact test was used to compare proportions. Non-normally distributed continuous data were analysed with the Mann-Whitney U test. A pre-specified \( \alpha \) of 0.05 was chosen. Odds ratios were used to depict the relative likelihood that patients with specified features would go on to have a biopsy that contributed to the diagnosis compared to the remainder of the cohort.

Results

Demographics and presentation

15, 620 neurosurgical procedures were performed during the study period. Keyword search and filtering revealed that 168 brain biopsies were performed in total during the study period (biopsies undertaken as part of resective oncology or epilepsy surgery were coded as the latter and therefore likely excluded from this figure). Of these, a total of 49 biopsies were performed on 47 patients (25 female) with cryptogenic neurological disease, at a mean age of 9.0 years (standard deviation 5.3). The two repeat biopsies were performed almost a year apart in both cases. The most common presenting symptoms were focal neurological deficit (28.6%), focal seizure (26.5%), and fever, obtundation or new movement disorder (all 20.4%), as shown in Figure 1A. Biopsy took place at a median of 90 days following symptom onset, with the shortest interval being 4 days; the longest after more than 5 years of indolent symptom course followed by a 2 year deterioration with increasing seizures and evolving focal neurological deficits. There was no statistically significant difference between time to biopsy from symptom onset and whether a diagnosis was reached at biopsy (Figure 1B). Whilst there was a shorter median time to biopsy in the second chronological half of the cohort compared to the first (90 vs 365 days), this difference was not statistically significant \( (p=0.411) \).

Prior to biopsy, children underwent a thorough investigative work up. The variation in presentation precluded a specific prescribed approach, but investigations were wide-ranging, including, but not limited to, serology for autoimmune encephalopathies and atypical infections, metabolic screening, bone marrow studies, white cell enzymes and biopsy of other organs, including skin, muscle and peripheral nerve. Children with suspected vasculitis underwent angiography; children with suspected inflammatory disorders underwent appropriate immunological (serum and cerebrospinal fluid (CSF)), thrombophilia and targeted genetic investigations, as determined by specialist paediatric neurologists. Children with suspected infections, in particular immune compromised patients, underwent extensive microbiological and virological testing on systemic and CSF samples as determined by paediatric infectious disease specialists, microbiologists and virologists. Brain MRI
was available in 42/47 patients; CSF sampling results were available in 40/47 patients and electroencephalography (EEG) was performed in 27/47 patients. Where MRI and CSF results were not available, these were cases occurring before the introduction of electronic patient records in our hospital. Examples of representative imaging from the cohort are shown in Figure 2. All these children were discussed in multidisciplinary clinical meetings, to ensure that wide expertise from multiple relevant specialties was available at every stage of their investigation.

The odds ratios (OR) depicted in Table 1 represent the relative likelihood that a patient in a given subgroup will yield a diagnosis on biopsy compared to the remainder of the cohort. Children presenting with focal seizures (OR 3.07, 95% confidence interval (CI) 0.63 – 15.0) were most likely to yield a diagnosis on biopsy. Diffuse MRI changes (OR 2.4, 95% CI 0.44-13.23) were most likely to lead to a diagnosis on biopsy.

The majority of referrals to neurosurgery were from neurology (n=35/49, 71.4%), with fewer referrals from infectious diseases (n=4/49, 8.2%), bone marrow transplant (n=4/49, 8.2%), immunology (n=1/49, 2.1%) and endocrinology (n=1/49, 2.0%) specialists. Four biopsies (n=4/49, 8.2%) were managed primarily by the neurosurgical team with input from other specialists. Twelve patients were immunocompromised; 7 had previously undergone organ transplant (6 bone marrow, 1 kidney). Immunosuppressed patients had a higher odds ratio (6.7, 95% CI 0.78-57.6) of yielding a diagnosis on biopsy, and a significantly higher odds ratio (5.8, 95% CI 1.4-23.9) of having an infective diagnosis determined on biopsy.

**Surgical procedure and morbidity**

The majority (27/49, 55.1%) of cases were performed through a small craniotomy; 19/49 (38.8%) stereotactically through a burr-hole, 2/49 (4.1%) endoscopically and 1/49 (2.0%) with robotic assistance. 19/27 open biopsies (70.4%) and 15/19 stereotactic biopsies (78.9%) yielded material which was contributory to diagnosis, but there was no statistically significant difference in these proportions (difference 8.5%, 95% CI -27.9% to 13.5%, p=0.735). Stereotactic biopsies were undertaken using a frameless technique. Biopsies from brains with normal MRI scans were taken from the right prefrontal region, anterior to the motor cortex, and no gross neurological deficits related to surgery were noted post-operatively. None of the biopsies performed endoscopically or robotically yielded material which was contributory to diagnosis. 39/49 (79.6%) biopsies were lobar/hemispheric, 6 midline and 4 of posterior fossa structures. In two patients (both in the most recent year of the current series), brain biopsy was performed as part of a stereotactic bilateral thalamic centromedian nucleus electrode implantation for refractory status epilepticus.

Three patients experienced moderate post-operative complications. One developed new post-operative focal seizures which were controlled with antiepileptic medication; one developed post-operative left hand weakness which resolved within 30 days; one developed a superficial surgical site infection treated with oral antibiotics in the community.

One patient, a 15-year old boy with thrombocytopenia, microangiopathy and immunosuppression due to a recent bone marrow transplant, suffered a a fatal post-operative intracerebral haematoma. He was being treated
for severe systemic candidiasis and showed limited response to the antimicrobial therapies given. A biopsy was performed, via a right frontal craniotomy, in order to confirm that the radiological lesions were indeed Candida, and to exclude any other pathology. On the first post-operative day a CT scan, performed in response to anisocoria, showed an ipsilateral intracerebral haematoma. Despite prompt evacuation of the haematoma, there was no improvement in the patient’s neurological status.

**Diagnosis and treatment**

Pathological analysis of biopsy material was contributory to diagnosis in 34 cases (69.4%). There was no statistically significant difference in the proportion of diagnostic biopsies in the first vs second half of the cohort ($p=0.495$). Pre-operative MRI diagnosis was concordant with final diagnosis in 45.7% of cases. Table 2 shows all final diagnoses and their frequency, and Figure 3 shows examples of the pathology seen at biopsy. Two patients underwent repeat biopsy a year apart: in one, chronic inflammatory changes were found on both occasions. In the other, an immunocompromised boy with previous bone marrow transplant, the first biopsy was inconclusive and he was clinically diagnosed with posterior reversible encephalopathy syndrome, the second identified aspergillosis.

Overall, infection (16/49, 32.7%) was the most common cause of cryptogenic neurological deterioration in this series. The most frequent organisms identified were *M. tuberculosis* (4 cases), Epstein-Barr virus (EBV; 3 cases), *T. gondii* and Aspergillus spp. (2 cases each), with 8/16 (50.0%) infective cases occurring in immunocompromised patients. Microbiological testing of biopsy material was contributory to diagnosis in several cases. In one patient, *A. fumigatus* was isolated on extended incubation of biopsy material, later confirmed on 18S PCR. The other case of aspergillosis (*A. delacroixii*) and two cases of toxoplasmosis were diagnosed on polymerase chain reaction (PCR) of biopsy material where CSF PCR studies prior to this had not yielded diagnoses. Epstein-Barr virus (EBV) was confirmed on tissue PCR in the context of histological changes consistent with EBV-driven inflammation (abnormal white matter, perivascular lymphocytic infiltrates) in 3 cases, in patients in whom EBV had already been identified on CSF studies but with uncertain significance, resulting in targeted treatment for this infection. Viral deep sequencing on lesional tissue identified astrovirus as the causative organism in a case of fulminant encephalitis in an immunocompromised patient. Histopathological analysis of brain biopsy material in this case had shown neuronal apoptosis with microglial activation, as detailed in our original case report1.

No organisms were identified in two patients with infective syndromes. One had meningoencephalitis in the setting of X-linked severe combined immunodeficiency and bone marrow transplantation, and was managed supportively. The other presented with focal seizures and had multifocal calcified lesions on CT scanning; biopsy revealed active chronic inflammation with granulomatous formation. The child was initially given antituberculous therapy but later switched to chronic granulomatous disease treatment, and eventually underwent bone marrow transplant.

In 38 cases, biopsy was felt to have altered clinical management of the patient (n=38/49, 77.6%). This includes cases where targeted antimicrobial therapy was instituted (8 patients); radiotherapy or chemotherapy was
instituted (5 patients); higher risk anti-inflammatory treatments were commenced (12 patients), and one case where these were avoided; further surgery was carried out (3 hemispherotomies for Rasmussen’s encephalitis); or referral to palliative care services were made (4 patients); 1 patient died; the remaining 4 patients were managed conservatively with the avoidance of higher-risk treatment modalities. There was no difference in the likelihood of biopsy altering clinical management between early (pre-2008) and late (post-2008) epochs of the cohort (Fisher’s exact test *p*=0.703).

**Discussion**

**Diagnostic yield and utility of brain biopsy**

Our data indicate that brain biopsy in children has a high diagnostic yield of 69.4% in children with neurological presentations that have defied diagnosis despite detailed clinical investigation. We found no statistically significant difference in the proportion of diagnostic biopsies in the early, as compared to the late, epoch of the current series. Results from retrospective series24 and a meta-analysis1 show diagnostic yields of 48.5% and 53.8%, respectively, in paediatric cryptogenic neurological disease. The diagnostic yields seen in older studies2,3,14 offer somewhat limited insight owing to the fact that modern day diagnostic techniques would have likely permitted earlier diagnosis through non-invasive means, such as extensive serological testing and better imaging modalities. However, we show in this contemporary series that even with the advent of high field MRI and genetic sequencing, a proportion of patients will continue to evade diagnosis, even with invasive methods such as brain biopsy.

The concordance of pre-operative MRI with final diagnosis was 45.7%; a similar finding was described in a recent UK cohort18. MRIs described as concordant were those which were specific to a single diagnosis and ultimately correct; many of the remainder provided a differential diagnosis which comprised the final diagnosis amongst others. However, in an extremely heterogeneous patient group, final diagnosis was often a composite of imaging, serological and biopsy information. MRI does remain an important staging post of investigation in this cohort, yet even within experienced clinical groups however, it rarely carries the certainty to allow consideration of new treatment options that may carry a higher risk. We show that biopsy often provides a definitive answer in these difficult cases.

The added value of a putatively diagnostic procedure lies in being able to prescribe treatment that otherwise would not have been offered. Thus, in our study, 77.6% (n=38/49) of biopsies were felt to have altered clinical management. This is slightly higher than other reports, in which biopsies alter management in 64.7%23, 67.1%1 and 71.9%24 of patients. These data suggest that brain biopsy offers real world clinical utility in the paediatric population. An added benefit of a biopsy-defined diagnosis in rare cryptogenic disease is that prognosis may be better defined, while offering to parents an explanation for their child’s neurological deterioration.

**Presentation and diagnoses**

The most common presenting symptoms and signs in this series were focal neurological deficit, focal seizure, and fever (Figure 1). Venkateswaran et al. found the most common presenting feature in their cohort was seizure activity (n=37/66, 56.1%)24, and that presentation with focal neurological deficits resulted in increased
likelihood of diagnostic biopsy. Our results replicate this, showing a higher odds ratio for diagnostic biopsy after presentation with focal seizures or focal neurological deficit, although the numbers in each group are small, and the 95% confidence interval crosses unity. We also found that diffuse MRI findings were more likely to lead to a diagnostic biopsy (OR: 2.4; CI 0.44-13.23). This may be due to more severe, fulminant cases with diffuse imaging changes possessing more florid pathology which is more easily appreciable on examination of biopsy material, as well as a greater ‘lesion burden’ amenable to biopsy.

We note that the population biopsied in the present study included several immunocompromised (n=12/47) and bone marrow transplant patients (n=7/12). Two-thirds of these patients were found to have infections based on microbiological and virological testing of brain tissue samples where CSF and systemic samples had not yielded a diagnosis, and had significantly higher odds of yielding an infective diagnosis from brain biopsy than their immune-competent counterparts (OR 5.78, with 95% CI > 1). Clinicians caring for immunocompromised patients with cryptogenic neurological disease may wish to consider biopsy early in order to confirm the presence of treatable organisms, narrow the number of antimicrobial drugs being given to a patient and determine total duration of treatment.

The most frequent diagnoses (Table 2) in the present study were infective (n=16/49, 32.7%), and the most frequent organism identified was *M. tuberculosis* (4 cases). In 3/4 TB cases, biopsy material was contributory to diagnosis in revealing necrotising granulomatous inflammation. In the fourth TB case (imaging shown in Figure 2A), biopsy ruled out malignancy – and was thus felt to have been contributory to clinical management – but did not show typical tuberculous lesions. The causative *Mycobacterium* was not identified on tissue culture, stains or PCR in any cases, thus patients were commenced on empirical anti-tuberculous therapy after exclusion of other granuloma-forming conditions, and all improved clinically. In all cases of toxoplasmosis and aspergillosis, diagnosis was made on microbiological studies of biopsy material where organisms had not previously been identified on CSF. Indeed, novel sequencing techniques mean that we are now more likely to obtain positive results of infection on brain biopsy samples when this has not been possible on CSF. This will become increasingly important as the burden of complex immune-suppressed patients rises.

Chronic inflammatory processes (20.4%)\textsuperscript{20}, and occult neoplastic disease (18.4%) were also common. The latter were always diffusely infiltrative lesions without a defined mass, therefore had defied accurate prior radiological diagnosis. Many of the diagnoses seen in this series, such as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPERS)\textsuperscript{19}, febrile infection-related epilepsy syndrome (FIRES)\textsuperscript{13}, astrovirus encephalitis\textsuperscript{4,27}, chronic or fulminant viral encephalitis\textsuperscript{15,16} have been reported in isolation. This report is able to set these rare diagnoses in the context of their clinical presentation in a wider paediatric cohort. The authors note that Venkateswaran et al. diagnosed a high proportion of vasculitis in their series (18.2%)\textsuperscript{24}, whilst our series had just one case, an ANCA-positive vasculitis in a 12-year-old girl presenting with hypertensive encephalopathy and acute visual loss.

*Surgical technique, safety and timing of biopsy*
The optimal timing of brain biopsy remains a challenging issue. Whilst the majority of biopsies in this series led to a definitive diagnosis and a change in clinical management, the risks associated with the surgical procedure – particularly in immunocompromised, myelosuppressed or coagulopathic patients – mandates that biopsy remains a last resort, to be considered after less invasive investigations are completed. Our practise has evolved throughout this series: in the latter half, biopsy was performed at a shorter interval following symptom onset (a median of 90 days compared to 365 days in the first half), with the shortest time to brain biopsy from symptom onset being 4 days (in a 1-year-old boy with obstructive hydrocephalus due to a posterior fossa mass lesion).

There is limited comparative data on time to biopsy in the literature. The recent paediatric series do not state length of time from patient presentation to biopsy. Our results showed no statistically significant difference between median time to biopsy stratifying by biopsy yield (contributory vs non-contributory). However, the data are heavily positively skewed, more so in the group without diagnostic yield, indicating that patients with the longest symptom courses eventually yielded negative biopsies in this clinical setting.

Brain biopsy is not a risk-free procedure, and these risks are increased in the immunocompromised population. In this study, there were 3 moderate complications, and one severe complication of death following post-operative intracranial haematoma in an immuno-suppressed and thrombocytopenic bone marrow transplant patient. In subjecting such complex patients such to brain biopsy, it should be acknowledged that there is a greater risk of serious complications. However, in such cases where the risk of death or disability is high due to the underlying organic condition, biopsy offers a last chance of diagnosis of a potentially treatable condition. Risk of postoperative neurological morbidity can be mitigated by biopsying lesions in non-eloquent sites. On the basis of our experience, biopsying non-lesional brains is safe and has utility; 1 of 2 samples from the right prefrontal cortex in patients with normal MRI scans resulted in a diagnosis, and did not cause any post-operative focal neurological deficit.

In this series, there was no significant difference in diagnostic yield for the two most numerous operative techniques deployed, open or stereotactic (70.4% vs 78.9%, p=0.735). The fact that none of the endoscopic or robotic biopsies yielded diagnostic material is likely due to a small sample size (n=3, combined). Different surgical techniques possess specific procedural-associated risks. For example, open biopsy may be safer than stereotactic biopsy as haemorrhage can be surgically controlled. However, it is important to appreciate that the reported risk of haemorrhage following brain biopsy in cryptogenic neurological disease is less than that in malignant disease.

Diagnostic nomenclature
The literature offers different levels of diagnostic ‘yield’ based on subjective rationale. Due to the rare nature of cryptogenic neurological disease and a lack of standardised reporting mechanisms, the definition of ‘useful’ biopsy is varied. For example, Rice et al. 2011 used ‘definitive’, ‘suggestive’ or ‘non-diagnostic’ from histopathological results based on the certainty of the likely diagnosis indicated in the neuropathologists report. In this report we took a pragmatic approach, classifying pathology reports as contributory to diagnosis if definitive or highly suggestive changes were noted. Venkateswaran et al. differentiates between ‘diagnostic’
and ‘diagnostic and useful’ based on its impact on management. Furthermore, another study demonstrated a low diagnostic yield of 29% due to their ‘strict’ definition of diagnostic material.

In paediatric cryptogenic neurological disease, establishing a diagnosis in order to institute disease-specific therapy is the primary scenario in which brain biopsy is useful. A second situation is to rule out malignancy or inflammatory conditions to permit further treatment, especially immune suppression. Finally, non-diagnostic brain biopsy can, in some situations, provide clinical utility, by excluding conditions which might require harmful treatment.

Limitations

Our study was retrospective in nature and therefore is subject to caveats of missing and incomplete data. For example, in many cases, it was not possible to discern the true extent of the biopsy. An ‘optimal’ brain biopsy sample – particularly in cases in which there was no focal radiological or macroscopic lesion – is a cubic centimetre of non-eloquent brain, including cortex and white matter as well as leptomeninges, and a small sample of dura (larger dural excisions can lead to complications in the form of CSF leak). It was difficult to deduce the total volume of our biopsy samples. During the 20 years that this study period encompasses, there have been significant advancements in diagnostic modalities, such as serological tests, PCR for infective agents and improvements in the quality of MRI. Tracking these changes to understand whether they had led to a reduction in the need for biopsy was not possible in this study. On the other hand, brain biopsy may now be considered a more useful tool now that samples can be subjected to more detailed testing, such as deep genetic sequencing for infective agents.

Conclusions

The present study evaluates the utility of brain biopsy in cryptogenic neurological disease in children. By definition, cryptogenic neurological disease remains a diagnostic conundrum. We have shown in this retrospective single-centre series, that there is utility in performing brain biopsy in this patient cohort: it is generally safe, has a high diagnostic yield and often directly influences management decisions. The timing of the biopsy remains a difficult and patient-specific issue, with the need to balance rapid neurological decline, thorough non-invasive investigation, surgical risk and local expertise. Logical infrastructure and clear communication in a multidisciplinary team is essential for decision making to ensure optimised treatment plans.

Ethical statement

Funding

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Conflict of Interest

There is no conflict of interest to report.

References


**Figure 1.** A, Barplot of presenting symptoms / signs and their frequency. B, Density plot of duration of symptoms prior to biopsy, in patients who had a diagnosis reached on biopsy and those who did not. Solid vertical lines show median symptom duration for two groups (both 0.2); dashed vertical lines show mean symptom duration for two groups, values indicated. *p* value shown for Mann-Whitney *U* test (data markedly positively skewed).

**Figure 2.** A, Pre-operative CT in a 12-year-old girl who presented with a 4-week history of headaches, vomiting and constitutional symptoms. Imaging was consistent with a diagnosis of tuberculous meningitis. Brain biopsy ruled out malignancy – and was thus contributory to clinical management – but did not show typical tuberculous lesions. The causative *Mycobacterium* was not identified on tissue culture, stains or PCR. She was commenced on empirical anti-tuberculous therapy and improved clinically. B, Axial T2 MRI in a 16-year-old boy with bone marrow transplant who presented with fevers and generalised seizures. Biopsy of the left parietal focal abnormality...
revealed toxoplasmosis. C, D, Coronal FLAIR MRI in a 14-year-old boy with a complex history of neonatal meningitis, epilepsy, and bone marrow transplantation 7 years earlier. He presented with headaches and arm weakness. Initially, the imaging differential was of multifocal demyelination (C); serial imaging showed progression of changes in the right diencephalon with an evolving differential towards neoplastic disease (D). Biopsy revealed gliomatosis cerebri, which can be appreciated on a scan taken 9 months post biopsy (E, F). E, coronal FLAIR MRI showing infiltration in the temporal, deep frontal lobe and right superior cerebellar peduncle; F, sagittal T1-contrast MRI showing enhancing lesions in the cerebellum, temporal lobe and thalamus.

Figure 3. Examples of the pathology found at biopsy. A, A biopsy that revealed a CNS Embryonal Tumour composed of diffuse sheets of hyperchromatic cells. B, A dural biopsy showing granulomatous inflammation characterised by necrosis (black arrowhead), epithelioid histiocytes (white arrowhead) and giant cells (arrow). C, Brain biopsy showing Toxoplasma gondii cysts (arrow) confirmed on immunohistochemistry (D). E and F show a brain biopsy from a patient with a fungal infection characterised by granulomatous inflammation, shown in E by the frequent giant cells (arrow) and fungal hyphae on Grocott staining F. Scale bars: 50um.

Table 1. Odds ratios for diagnostic biopsy given presenting symptoms/signs and MRI findings. *, denominators do not add up to 49 as many patients presented with more than one symptom/sign. §, denominators total 42, as MRI reports and images unavailable in 5 patients.

<table>
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<tr>
<th>Symptom/Sign</th>
<th>OR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Headaches</td>
<td>3.5 (2.1-5.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>Arm weakness</td>
<td>2.0 (1.2-3.3)</td>
<td>0.008</td>
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OR: odds ratio; CI: confidence interval.

Table 2. Final diagnoses and frequency. ADEM, acute disseminated encephalomyelitis; CLIPERS, Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids; DNET, dysembryoplastic neuroepithelial tumour; FIRES, febrile infection-related epilepsy syndrome; PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosus.
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<th>Diagnostic Biopsy</th>
<th>OR</th>
<th>95% CI</th>
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<td>Headache</td>
<td>3/5</td>
<td>0.71</td>
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<td>Fever</td>
<td>6/10</td>
<td>0.69</td>
<td>0.18 – 2.68</td>
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<td>Focal seizures</td>
<td>11/13</td>
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<td>0.63 – 15.0</td>
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<td>0.02 – 2.62</td>
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<td>0.27 – 4.83</td>
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<thead>
<tr>
<th>MRI findings §</th>
<th>Diagnostic Biopsy</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1/2</td>
<td>0.48</td>
<td>0.03 – 8.32</td>
</tr>
<tr>
<td>Diffuse (&gt;3 lesions)</td>
<td>8/10</td>
<td>2.4</td>
<td>0.44 – 13.23</td>
</tr>
<tr>
<td>Multifocal (2-3 lesions)</td>
<td>10/17</td>
<td>0.56</td>
<td>0.15 – 2.04</td>
</tr>
<tr>
<td>Focal (single lesion)</td>
<td>9/13</td>
<td>1.18</td>
<td>0.29 – 4.83</td>
</tr>
</tbody>
</table>

Table 1. Odds ratios for diagnostic biopsy given presenting symptoms/signs and MRI findings. *, denominators do not add up to 49 as many patients presented with more than one symptom/sign. §, denominators total 42, as MRI reports and images unavailable in 5 patients. OR: odds ratio; CI: confidence interval.
Table 2. Final diagnoses and frequency. ADEM, acute disseminated encephalomyelitis; CLIPPERS, Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids; DNET, dysembryoplastic neuroepithelial tumour; FIRES, febrile infection-related epilepsy syndrome; PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Biopsy contributory to diagnosis (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>4</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>T. gondii</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>3</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>No organism identified</td>
<td>2</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>S. pneumococcus</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Astrovirus encephalitis</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td>3</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>DNET</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Germinoma</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Poorly differentiated malignant leptomeningeal tumour</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Rasmussen’s encephalitis</td>
<td>4</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chronic inflammatory lesions</td>
<td>10</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>CLIPPERS</td>
<td>1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>FIRES</td>
<td>2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PRES</td>
<td>1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>34 (69.4%)</td>
</tr>
</tbody>
</table>
Focal neurological deficit
Focal seizures
Coma
Movement disorder
Generalised seizures
Fever
Headache
Hydrocephalus