The Role of Biopsy in the Diagnosis of Infections of the Central Nervous System

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Abstract
CNS infections require prompt appropriate therapy, but do not usually require tissue biopsy for diagnosis. We performed a 5 year audit of CNS infections which required brain or spinal biopsy to determine or confirm a diagnosis of CNS infection. Sixteen cases were identified in which clinical, radiological or additional investigations including culture, serology or PCR for the suspected specific infective agents were not diagnostic. 6 (37.5%) were bacterial abscesses presenting as space-occupying intracranial lesions with a differential diagnosis of neoplasm. There were 3 (18.7%) cases of toxoplasmosis and 2 (12.5%) cases of aspergillosis. There was one case (6.2%) of herpes simplex encephalitis, one cytomegalovirus and one progressive multifocal leukoencephalopathy, all biopsied as possible neoplasms. There were 2 (12.5%) cases of spinal tuberculosis, one multifocal, mimicking neurofibromatosis. This review highlights the usefulness of targeted biopsy in the rapid diagnosis of CNS infections. It also emphasizes the lack of specificity of negative culture and serology in certain cases, especially in the setting of immune-compromise.

Introduction
In spite of advances in therapy, the morbidity and mortality caused by infections of the central nervous system (CNS) continue to be high. The rate and types of infection have been influenced by factors such as trauma, neurosurgical intervention and invasive monitoring, international travel, immigration and increasing numbers of patients who live with immune compromise. The majority of CNS infections are diagnosed by conventional microbiological methods including microscopy and culture, serology and more recently, various molecular techniques, especially in the detection of viral infection.

In our practice at Cork University Hospital, a regional neurosciences centre, a number of cases came to attention where neurological biopsy was necessary for the diagnosis of infection in spite of appropriate other investigations.

Methods
Neuropathology reports from 01/01/2004 to 31/12/2008 were reviewed and all biopsies where CNS infection was diagnosed were identified. The case notes and microbiological investigations performed for each patient were reviewed. The majority of biopsy material was examined intra-operatively by smear or frozen section and after fixation in 10% buffered formalin on haematoxylin and eosin stained slides cut at 3µm. Where appropriate, additional stains were performed, including Gram, Gomori methenamine silver, Periodic Acid Schiff and Ziel-Halliciou as well as immunohistochemistry for intra alia toxoplasma, SV 40 antigen, CMV and herpes simplex virus types 1 and 2.

Results
Sixteen cases of CNS infection were identified (Table 1). Thirteen patients were male and 3 were female. The age ranged from 17 to 77 years. Six patients were from outside Ireland, 3 from Africa and 1 each from the Indian subcontinent, Eastern Europe and South America. Four patients were immunocompromised and all had opportunistic infections. The requirements for immune compromise included HIV disease (1), treated haematological malignancy (2) and treated sarcoidosis (1). The opportunistic infections were toxoplasmosis (2 cases), progressive multifocal leukoencephalopathy (PML) due to JC virus (1) and Aspergillus fungal infection (1).

Six cases were abscesses (presumed bacterial). In 3 of these an organism was isolated, 2 Gemella haemolysans and 1 Serratia liquefaciens. In the remaining 3 cases, an organism was not isolated. Of these, 2 were culture negative but had typical histological features and one had received antibiotics prior to surgery. The third case did not have tissue submitted for culture. In 5 cases the biopsy was performed to confirm abscess and exclude the radiological differential diagnosis of tumour. In 1 case the operation was performed to relieve increasing intracranial pressure. There were 4 paracoccid infections, 3 protozoa (all Toxoplasma gondii) and 1 cestode (Taenia solium). In each case of toxoplasmosis, the definitive tissue diagnosis was in the clinical and radiological differential diagnosis. However, serology (IgM) was negative in all 5. Toxoplasma dye tests and polymerase chain reaction (PCR) performed on blood in 2 cases were negative. The Taenia solium neurocysticercosis case presented with new onset seizures and the lesion identified was radiologically thought to be either tumour or tuberculoma.

Discussion
Bacterial infections of the CNS continue to be life-threatening and often have serious sequelae. Abscesses have non-specific symptoms and signs and evidence of local or systemic infection is often lacking. Imaging may distinguish abscess from tumour although the differential diagnosis of other causes of mass lesions remains. Gemella haemolysans is a facultative anaerobic Gram-positive coccus, forming part of the normal flora of the mouth and upper respiratory tract. It is a very rare bacterial isolate in brain abscesses.

Published case reports of patients with systemic Gemella abscesses often implicate a dental contamination point and cases of disseminated infection are often associated with co-morbid conditions including immune compromise, cancer, heart disease and poor oral hygiene. TB remains a common disease of developing countries, for various reasons, including immigration, there has been resurgence in developed countries.

Tuberculosis, i.e. tumour-like mass lesions of tuberculosis are well described in the CNS and are thought to arise when tuberculocanuloma enlarge in

Figure 1. Cervical sagittal T1 weighted MRI scan showing a mass (arrow) at C6/7 intervertebral foramen.

There were 2 fungal infections, each Aspergillus. Neither was confirmed by culture in spite of fresh material in which fungi were identified by rapid intraoperative immunofluorescence.

Figure 2. Herpes simplex encephalitis. (A) A cortical neurone with an intracytoplasmic eosinophilic inclusion (arrow) distending the cell. H&E 400x. (B) Brown cytoplasmic signal in infected neurones (arrow) indicating virus antigen. Immunostain for Herpes simplex virus 400x.

The diagnosis was not suspected clinically and the radiological impression was of infiltrative neoplasm. Consequently CSF viral studies were not performed prior to biopsy. The PML case was clinically and radiologically suspected, but JC virus studies (PCR on CSF and serum) were negative. In spite of this, numerous infected oligodendrocytes with typical viral inclusions were positive with in situ hybridisation were present (Figure 3). Of interest, biopsies of 2 cases of radioactively suspected herpes simplex encephalitis during the study period were infiltrating malignant gliomas. There were no non-diagnostic biopsies of suspected infective lesions in the study period.

Figure 3. Progressive multifocal leukoencephalopathy. (A) White matter showing enlarged smudged oligodendrocyte nucleus (arrow) indicating viral inclusion. H&E 400x. (B) Brown nuclear signal in oligodendrocyte nuclei indicating PML virus antigen. In situ hybridisation for SV40 virus 200x. SV40 cross reacts with JC virus.

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laminectomy or brain tissue without rupturing into the subarachnoid space. Tuberculomas of the spine are very rare and may be extradural, intradural or intramedullary. Most cases of spinal tuberculoma in the literature are diagnosed by biopsy.

Fungal infections of the CNS, once thought to be rare, are increasing in frequency because of increased incidence of immune compromise and overuse of antifungal chemotherapy. Biopsy material is often not available for culture. It is a challenging diagnosis for the microbiology laboratory although an increasing armamentarium of serologic tests, including assays for serum beta glucan and galactomannan, seeks to address this problem. In practice, the ability of frozen section to provide rapid diagnosis allowing quick institution of therapy is the failure of isolation by culture in both cases is difficult to explain. However, the characteristic microscopic morphology permitted species identification, although information about sensitivity was lacking.

Cysticercosis remains a serious public health problem in developing countries. The most common manifestation of neurocysticercosis is seizures, occurring in up to 90% of cases. Our case highlights the problem presented by migrant populations with negative serology. The combination of characteristic imaging, especially if anti-Toxoplasma IgG antibodies are present, is considered sufficient to start empiric therapy in the absence of positive serology and with negative PCR on CSF illustrates that biopsy remains the gold standard for diagnosis.

In summary, this study highlights the continuing role of biopsy in the diagnosis of CNS infections. In 13 of 16 cases diagnosis relied on biopsy and in 4, biopsy was essential even though the causative organism was specifically looked for by other methods. It is likely that the need for targeted biopsy may increase due to factors such as immigration from developing countries and increasing numbers of immunocompromised patients. The study also underlines the importance of considering infective lesions of the CNS when investigating space-occupying lesions and has safety implications for pathology laboratories when making smears or cutting frozen sections on fresh tissue submitted for intra-operative diagnosis.

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References


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