Infections of the central nervous system

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Abstract

The brain can be infected by innumerable agents from prions to worms. Most diagnoses are made by microbiology following clinical and imaging investigations. Pathologists get involved with biopsies and autopsy scenarios; many are straightforward but some are difficult, and we must involve microbiology — including molecular diagnostics — appropriately. Optimum protocols of sampling need to be developed for meningoencephalitis diagnostics. New scenarios of infectious encephalitis are still emerging, e.g. with changing treatment for HIV disease. The autoimmune encephalitides are emerging as a major differential diagnosis with infection.

Keywords brain infections; diagnostic; encephalitis; HIV; meningitis; parasites; rabies; tuberculosis

Introduction

The central nervous system (CNS) comprises the brain, spinal cord, meninges, and the nerve roots emerging from the cord. All varieties of infectious disease (ID) agents can damage the CNS: viruses, prions, bacteria, mycobacteria, fungi, protozoa, helminths, pentastomes, and arthropods.

A comprehensive account of all these is not possible here, so the emphasis is on general principles of CNS infection, some important diseases in the main ID groups and differential diagnosis. Selected difficult cases from autopsy and biopsy casework highlight diagnostic issues.

Information resources on infections and their agents

A general textbook of the clinical pathology of all infectious diseases in man, including those affecting the CNS, is that edited by Connor and Chandler.[1] The standard comprehensive textbook — regularly updated — on clinical, taxonomic, diagnostic and treatment aspects of infectious disease is that by edited by Mandell, Bennett and Dolin.[2] New information on how to diagnose fungal infections on histology is from Guarner et al.[3]

Gutierrez's comprehensive monograph on all parasitic infections' pathology contains a lifetime of experience.[4] The now-defunct USA Armed Forces Institute of Pathology published a comprehensive illustrated text on the pathology of helminths (worms).[5] The related Defense Technical Information Center has recently issued, online only, a parallel text on the pathology of protozoa and arthropods.[6] The World Health Organisation (www.who.int) also provides up to date epidemiological data on the major parasitic infections. Parasite life cycles, as well as much relevant epidemiology, are published online by the USA Centers for Disease Control and Prevention (CDC). (www.cdc.gov). *Greenfield's Neuropathology* covers all the important agents.[7]

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Principles of CNS infections

The main determinants of the outcome when a pathogen enters the CNS are its virulence, the state of the host's immune system, and how it got there.

Routes of infection into the central nervous system

The route for the standard CNS infections (bacterial meningitis, cryptococcosis, toxoplasmosis, worms) is blood-borne (Box 1).

Host immune status

Some infections are innately virulent and cause damage directly (e.g. HSV); others depend on the host response to do much of the pathology (e.g. tuberculosis, some patterns of HIV encephalitis). Thus the status of host resistance (innate and immune/acquired) is critical in determining the outcome of an infection in the CNS. The relevant factors include:

- age
- genetic predisposition
- immune status, e.g. HIV infection, malnutrition, iatrogenic immunosuppression
- specific immunity
  - active — previous exposure, vaccination
  - passive — antibodies from mother or introduced iatrogenically
- trauma/surgery/foreign body.

Diagnostic approaches for CNS infection

It is important for clinicians and pathologists to consider the actual clinical scenario since the pattern of disease determines what can be the possible causes — meningitis, meningoencephalitis, encephalitis or encephalopathy, myelopathy/myelitis, ependymitis, and radiculopathy. Imaging is undoubtedly important in limiting the range of diagnostic possibilities,

The three routes by which infectious organisms reach the CNS

- Blood-borne
  - Across the blood—brain barrier
  - Across the blood—CSF barrier
- Neural — travelling along nerves, centripetally
  - Rabies
  - HSV and VZV
- Direct invasion
  - Via nasal or ear sinuses
  - Traumatic implantation through the skull

Box 1

but must not be taken as absolute — the pictures can only indicate the pattern of disease, not the cause; similarly molecular diagnostics, whilst helpful and increasingly essential in specifying many infections can also mislead through poor specificity and sensitivity.

Brain biopsy is often considered a process of last resort, which is unfortunate since much investigative time and expense may be avoided with judicious use of biopsy early in the diagnostic process. The non-biopsy modalities are listed in Box 2.

Histopathologists use standard fixed tissue histopathology for considering CNS infections. But there is great potential for rapid and accurate ID diagnostics using dab cytology of fresh brain tissue (as with suspected tumours — see Figures 9 and 10 below). Over the last two decades, the range of useful immunohistochemical (IHC) reagents for IDs that work on formalin-fixed paraffin-embedded tissue has expanded enormously. Commercially or in special centres[8] there are antibodies for all the standard virus infections, some bacteria and fungi, and many protozoa. IHC is not much use for worm infections; for them, as for all the types of ID agents, PCR improves in its application annually.

Differential diagnosis of CNS infection

Despite appearing to be infection, many CNS disease histopathologies have other pathogeneses (e.g. granulomas and vascular inflammation). Box 3 indicates non-ID conditions that can simulate an infection, and must be considered when ID options are exhausted.

Specific clinico-pathological scenarios

Viral encephalitis

'Encephalitis' has many causes but a more limited range of pathological appearances. The standard histology is of:

- perivascular lymphocyte accumulation
- diffuse parenchymal lymphocyte infiltration
- neuronophagia, i.e. destruction of neurones [this is variable].

Diagnostic modalities in CNS infections

- CSF examination
  - Culture
  - Serology
  - Molecular technology e.g. PCR
- Blood sampling
  - As for CSF
  - Autoimmune encephalitis serology and PCR studies
  - HIV viral load etc
- Imaging, with CT, MRI, PET scans etc
- Empirical chemotherapy treatment (often used for suspected but non-proven HSV encephalitis, tuberculous meningitis and toxoplasmosis)

Box 2

Differential diagnosis of CNS infection

- Haemorrhage
- Malignancy and benign tumour
- Ischaemic and vasculitis syndromes
- Autoimmune mediated encephalitis
- Drug and chemical induced
- 'Post-infectious' syndromes
- ADEM (acute demyelinating encephalomyelitis)
- Vaccination encephalitis
- Granulomatous inflammation with the CNS can be:
  - Neurosarcoidosis vs TB
  - Reaction to nearby germ cell tumour
  - Component of vasculitis, +/− eosinophilis

Box 3

The lymphocytes are characteristically CD8 + T-cells; there are usually fewer or no CD4 + T-cells or B-cells. It is important to remember that the normal brain contains no parenchymal T-cells, hence their identification is critical for a diagnosis of "? encephalitis".

In addition, there may be:

- necrosis and haemorrhage
- microglial cell activation and accumulation
- astrocytic activation
- variable plasma cell and eosinophil infiltration
- viral inclusion bodies in brain cells' cytoplasm or nuclei, or in endothelial cells
- parenchyma oedema and cerebral swelling.

The diagnosis depends thus on the integration of:

- clinical features with imaging (i.e. pathology location)
- which parts of the CNS are involved
- the histopathological pattern
- the identification of visible ID agents, or their identification with IHC and ISH
- ID identification with PCR on fresh or fixed CNS tissue
- serology for certain diseases.

Encephalitis without further qualification is usually considered to be viral in aetiology. The causes vary greatly in different parts of the world. In the UK the common causes are:

- enteroviruses, which include:
  - coxsackieviruses
  - enteroviruses (e.g. EV 68—71)
  - echoviruses
- mumps virus
- herpes simplex viruses (genital herpes)
- HIV seroconversion illness
- other herpes viruses

  e.g. varicella zoster virus
  Epstein Barr virus
  HHV6.

Typical EV71 encephalitis (Figure 1) shows inflammation in all parts of the brain (grey and white matter) and the triad of histopathology. Confirmation of the cause relies on PCR of CSF or tissue. Pathologists are more likely to see this type of encephalitis than the more common herpes encephalitis, since the latter has