Inflammatory Diseases of the CNS I: Encephalitis

Introduction
Intracranial infections involving the bones of the skull or spine (osteomyelitis), the extradural compartments, the pachymeninges (dura), subdural space, leptomeninges and subarachnoid space are mainly caused by bacteria and occasionally by fungi and viruses (leptomeningitis). The organisms that infect the CNS itself (the brain and the spinal cord) are mainly viruses and bacteria, but fungi and protozoa, such as Toxoplasma and amoebae, do occasionally invade the CNS. Encephalitis can be defined as diffuse inflammation of brain tissue, or spinal cord (encephalomyelitis or just myelitis). Two major forms of encephalitis occur: those due to virus infections and those due to autoimmune inflammation - Acute Disseminated Encephalomyelitis (ADEM).

Viruses responsible for encephalitis
The table lists the main viruses involved in encephalitis and encephalomyelitis. Many are enteroviruses; encephalitis caused by respiratory viruses appears to be less common. In many parts of the world encephalitides are seasonal due to the spread of viruses by insects (arboviruses). New virus infections of the CNS, such as West Nile Fever and Nipah, continue to evolve.

Immunosuppression is an important predisposing factor for infections of the central nervous system by viruses such as the wart virus (papova virus). Viruses mainly gain access to the body via the respiratory, gastrointestinal or genitourinary mucosae and through insect bites. From the site of inoculation, viruses spread to lymph nodes and then enter the brain via the blood. Certain viruses, e.g. rabies, enter the CNS by retrograde axoplasmic transport along nerves from peripheral wounds. Other viruses, such as human immunodeficiency virus (HIV), are thought to enter the CNS within infected mononuclear cells/macrophages. DNA viruses (eg herpes simplex) and RNA viruses (eg measles) enter neurons and glia by attaching to receptors on the cell surfaces and then replicate within the cell. New virus particles may bud from the surfaces of cells or are released through lysis of the infected cells. In autoimmune encephalomyelitis (ADEM) there is no causative virus in the CNS, although the inflammatory changes of perivascular inflammation and perivascular demyelination may be widespread and are thought to result from an autoimmune reaction, frequently in response to a previous systemic virus infection.

Pathology
The pathology of the various viral infections listed in the

Table: Viruses causing encephalitis in various regions of the CNS (modified from 1)

<table>
<thead>
<tr>
<th>Viruses infecting the central nervous system and its coverings</th>
<th>Meningitis</th>
<th>Virus affecting mainly grey matter (pontoencephalitis/pontomyelitis)</th>
<th>Virus affecting mainly grey matter (leukoencephalitis or leukoencephalopathy)</th>
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</thead>
<tbody>
<tr>
<td>Echovirus, Coxsackievirus, Other enteroviruses, Diphtheria</td>
<td>Papovavirus (JC virus)</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Herpes simplex virus 2 Mumps Human immunodeficiency virus</td>
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<td></td>
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<tr>
<td>Lymphocytic choriomeningitis virus</td>
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<td></td>
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<tr>
<td>Virus affecting mainly grey matter (polioencephalitis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poliovirus, Echovirus 4, A7 or B3</td>
<td>Herpes simplex virus 1, Herpes simplex virus 2</td>
<td>Varicella-zoster virus</td>
<td></td>
</tr>
<tr>
<td>Enteroviruses 70 and 71</td>
<td>Cytomegalovirus</td>
<td>Human immunodeficiency virus</td>
<td></td>
</tr>
<tr>
<td>Rabies, Arboviruses</td>
<td>Measles</td>
<td></td>
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</tbody>
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Professor Roy O. Weller has wide experience in providing a regional diagnostic neuropathology service in Southern Britain and has published a number of textbooks. His research fields have been in peripheral neuropathies, hydrocephalus and tumours, and more recently in Neuroimmunology and Alzheimer’s Disease.
table varies, depending upon the causative virus, the location in the brain or cord affected and upon the acute or chronic nature of the disease. For example, poliomyelitis classically infects and destroys spinal and bulbar motor neurons, whereas herpes simplex infection (HSV-1) is localised to the temporal lobes. Nevertheless, the major pathological reactions within the CNS are very similar throughout a whole range of virus infections. As an example of an acute encephalitis, the pathology of herpes simplex encephalitis is described in some detail below.

Herpes simplex (HSV-1) encephalitis is probably the most common acute necrotising encephalitis in the UK. Patients present with headache, fever, seizures and decreasing levels of consciousness. CT and MRI reveal swelling and necrosis of the temporal lobes that is often bilateral. In patients who survive for many years, there is cystic change and atrophy of the temporal lobes. HSV is present in cold sores on the lips and in the trigeminal ganglia; but whether the close anatomical relationship between the trigeminal ganglia and the temporal lobes plays a role in the spread of infection to the brain remains unresolved.

Macroscopically, the brain at autopsy in a patient dying with acute herpes simplex encephalitis shows haemorrhage, swelling and necrosis of the temporal lobes (figure 1a), often with atrophy and cystic change.

The diagnostic features of encephalitis are seen microscopically. They consist of death of neurons and other cells, inflammation and the presence of the infecting virus. Dying neurons are recognised by their shrunken (pyknotic) nuclei, and pale, pink cytoplasm in haematoxylin and eosin (H&E) stained sections. The major inflammatory cells are lymphocytes; they enter the brain via post-capillary venules, accumulate around veins and spread diffusely into the infected brain tissue (Figure 1b). Microglial cells become activated, proliferate and may form small collections (microglial stars) around dead virus-infected neurons that they ingest (neuronophagia) (figure 1c). A small number of neutrophil polymorphonuclear leukocytes may be present in the early stages of the disease whereas reactive astrogliosis and macrophages are seen in the more advanced stages of the encephalitis. Identification of HSV-1 in the tissue allows a definitive diagnosis to be made. This may entail the culture of virus or the detection of antibodies to HSV in the CSF; more commonly now, viral DNA is detected by PCR.

Viruses are detected in biopsy or autopsy brain tissue...
in a variety of ways. Virus particles can be isolated by homogenising fresh tissue in glutaraldehyde, centri fuging and negatively staining the virus in the supernatant with phosphotungstate (figure 1d); this was a major diagnostic technique before the introduction of immunocytochem istry and PCR, and remains a key investigation for the characterisation of novel virus infections. In H&E-stained sections of brain tissue, viral inclusions may be seen in the nuclei of infected cells, or the virus may be spread more diffusely through the nucleus (figure 1e). Viral particles in the nuclei lack the outer membrane of the intact virus (compare electron micrographs figure 1d and f). Viral proteins within cells are detected by immunocytochem istry (figure 1g), provided the antibodies are available, and viral DNA by in situ hybridisation (figure 1h).

The pathological features illustrated in figures 1 b & c are characteristic of the body’s defences against virus infections. Infected cells produce interferons (IFN). IFN-β are characteristic of the body’s defences against virus infections. IFN-γ do not normally infect the CNS, such as cytomegalovirus (CMV) and papova virus, may proliferate in the CNS causing CMV-encephalitis and progressive multifocal leukoencephalopathy respectively.

**Differential diagnoses**

One major differential diagnosis at biopsy or autopsy is between virus infection and autoimmune encephalomyelitis (ADEM). The regional specificity of many virus infections within the CNS may suggest a diagnosis of viral encephalitis as may the intense lymphocyte infiltration and presence of viral protein or nucleic acid by histology, immunocytochemistry and in situ hybridisation. PCR or antibody studies of CSF may identify a virus. However, in more than 50% of cases no virus is identified by these techniques even though it is suspected. ADEM is usually preceded by a systemic viral illness some 2-3 weeks previously, such as measles in the developing world or a wide variety of pulmonary or gastrointestinal infections in Europe and USA. Although often centred on the cerebral white matter, ADEM may affect many areas of the CNS including the spinal cord. Distinction from a virus infection may be difficult and may depend upon the history and the lack of evidence of a virus infection in the CNS. Bacterial and fungal infections mainly result in neutrophil polymorphonuclear leukocyte infiltration and focal necrosis associated with the presence of bacteria or fungi. Differentiating these diseases from the lymphocyte-dominated inflammation of viral encephalitis and ADEM is, therefore, relatively straightforward. The other major differential diagnosis is multiple sclerosis (MS). MS appears to be an autoimmune disorder and is characterised by demyelination, perivascular lymphocytes, microglial activation, monocyte/macrophage invasion reactive astrocytosis, and varying degrees of axonal degeneration. However, MS plaques are usually focal and well-demarcated areas that lack overt evidence of infecting virus. Confusion occurs most often between MS and ADEM, although mostly the MS plaques are well circumscribed whereas the areas of demyelination seen in ADEM are frequently confined to narrow areas around veins.

**References**


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