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Encephalitis, Viral
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Introduction

Encephalitis refers to the inflammation of the brain. The term includes both viral infections of the brain with predominantly gray matter disease and acute disseminated encephalomyelitis (ADEM), an immune-mediated demyelinating disease. In addition, other immune-mediated forms of encephalitis associated with antibodies to voltage-gated potassium channels, or N-methyl-D-aspartate (NMDA) receptors, are being recognized with increasing frequency; being not viral associated, they are not discussed further here. Clinically, acute viral encephalitis and ADEM usually manifest with fever, severe headache, neck stiffness, alterations of consciousness, focal neurological signs, and often seizures, especially in children. The pathology of acute viral encephalitis is characterized by mononuclear inflammatory cells in a perivascular distribution in the gray matter and meninges and neural cell destruction with neuronphagia. The pathology of ADEM or postinfectious encephalomyelitis is characterized by perivenular mononuclear cell inflammation and demyelination predominantly in the white matter of the brain and the spinal cord. Both forms of encephalitis are linked primarily with viral infections, but both are also associated with some bacterial infections. Rarely, acute encephalitis may be due to fungal and parasitic infection, and ADEM may be associated with vaccines. The two forms of encephalitis occur because of different spectra of viruses and involve different mechanisms of pathogenesis. Following some general comments on viral pathogenesis, the two forms of encephalitis are discussed separately.

Pathogenesis

Viruses can be released by infected humans or animals in saliva, respiratory droplets, breast milk, feces, urine, semen, vaginal secretions, blood, or tissue. Viruses have no mobility but must penetrate strong barriers to enter the body of a susceptible human host. The skin is covered by a layer of keratinized cells that will not sustain virus replication, but arthropods and animal bites, needles, and tissue transplantation can breach this barrier directly (Table 1). The mucous membranes of the respiratory, gastrointestinal, and genitourinary tract are protected by secretory immunoglobulins (Ig), and all are monitored by macrophages that phagocytize viruses and other particles. In addition, the respiratory tract has a mucus coating and cilia that beat the film containing inhaled particles outward and away from the epithelial cells of the lower respiratory tract, and the gastrointestinal and genitourinary tracts have extremes of acidity. A few noneveloped, acid-resistant viruses (adenoviruses, enteroviruses, paroviruses, and reoviruses) can survive passage through the acidity and solvents of the gastrointestinal tract.

Once permissive host cells are infected in the subcutaneous tissue, the mucous membranes, or the hematopoietic system (particularly macrophages), viruses replicate usually locally before there is invasion of the central nervous system (CNS). Spread into the CNS is via nerves or the blood (Table 2). For many years, the nerves, both peripheral and olfactory, were regarded as the sole portals into the CNS, and early experimental studies documented the neural transmission of rabies virus, herpes simplex virus, and polioviruses. Nerve endings have receptors for some viruses, and the viruses are

Table 1 Entry for viruses causing human viral encephalitis

| Route of entry in natural infection | Viruses |
|-----------------------------------|---------|
| Inoculation                       | Arboviruses |
| Animal bite                       | Rabies virus |
| Blood transfusion                 | Herpesvirus simiae |
| Transplantation                   | Cytomegalovirus |
| Intentional                       | Hepatitis B virus |
| Respiratory                       | Human immunodeficiency virus |
| Droplet                           | Human T-cell lymphotropic virus |
| Saliva                            | Rabies virus |
| Enteric                           | Creutzfeld–Jakob disease |
| Venereal                          | Vaccine viruses |
| Transplacental                    | Mumps virus |
| Source                            | Minyamard human encephalitis |

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transported by the retrograde axon transport system to the cell bodies, where replication is possible. This transport occurs in the peripheral nervous system along motor and sensory fibers and also within the CNS, exemplified by the movement of polioviruses between spinal cord motor neurons and corresponding cortical neurons. The olfactory pathway is a unique venue for neural spread because the olfactory rods extend out from the olfactory mucosa and the central processes of the olfactory neurons synapse within the CNS. Thus, a single neuron can provide transport from the ambient environment to the CNS. Despite this direct connection, few aerosol or respiratory infections have been found to invade through the olfactory route.

Although early studies concluded that the blood–brain barrier was impenetrable by viruses, most viruses do invade the CNS from the blood. Some viruses infect cerebral endothelial cells or choroid plexus epithelial cells and ‘replicate before spreading’ into the CNS. Others cross uninfected vascular endothelial cells into the brain in endocytotic vesicles or within infected mononuclear cells (e.g., human immunodeficiency virus (HIV)). Invasion from blood depends on the magnitude and duration of the viremia. Viruses in the blood are promptly removed by the reticuloendothelial system and, similar to other particles, speed of clearance is size dependent. Small viruses (e.g., flavivirus such as the West Nile virus) are removed more slowly, and many larger viruses avoid clearance by growth in leukocytes or adhesion to red cells.

Within the CNS, specific cell populations may be vulnerable to specific viruses. For example, rabies virus infects only neurons, and early in infection neurons that modify behavior are selectively affected. This explains the unique clinical syndrome of vigilance and agitation. Similarly, polioviruses selectively infect and destroy motor neurons causing the syndrome of flaccid paralysis. Arboviruses infect primarily neurons, especially in the basal ganglia, and herpes simplex virus infects neurons, glia, and endothelial cells. JC virus selectively lyses oligodendrocytes causing demyelinating disease. Enteroviruses and mumps virus infect primarily meningeal and ependymal cells; therefore, they usually cause benign meningitis and only rarely are associated with encephalitis.

Neuroinvasiveness, neurotropism, and neurovirulence are features of viruses that need to be differentiated. Neuroinvasiveness is the ability to penetrate the CNS. Traditionally, neurotropism referred to the ability to infect neural cells other than neurons and is distinct from neuronotropism, which indicates the ability to infect neurons; however, in more recent literature, the term neurotropism is applied to both types of infection. Neurovirulence relates to the ability to cause disease. Thus, mumps virus that can often be recovered from spinal fluid during uncomplicated parotitis is highly neuroinvasive, is neurotropic in ependymal cells but not neuronotropic, and has a low level of neurovirulence. In contrast, most arbovirus infections are asymptomatic or cause only fever, malaise, and minor systemic symptoms. On rare occasions when arboviruses infect the brain, they usually cause encephalitis with a significant death rate; thus, these viruses are not highly neuroinvasive but are highly neurotropic (and neuronotropic) and neurovirulent. It must be noted that

| Pathway    | Experimental hosts                                      | Natural disease of humans                                      |
|------------|--------------------------------------------------------|----------------------------------------------------------------|
| Neural     | Herpes simplex virus                                   | Rabies virus                                                   |
|            | B virus                                                | Herpes simplex viruses                                         |
|            | Rabies virus                                           | Varicella–zoster virus                                          |
|            | Polioviruses                                           | Herpes simiae (B virus)                                        |
|            | Reovirus, type 3                                       | Polioviruses                                                   |
|            | Bornavirus                                             |                                                              |
|            | Scrapie agent                                          |                                                              |
|            | Creutzfeldt–Jakob disease agent                        |                                                              |
| Olfactory  | Herpes simplex virus                                   | ?Herpes simplex virus, type 1                                  |
|            | Polioviruses                                           | Aerosol infections with rabies and arboviruses                 |
|            | Arboviruses                                            |                                                              |
|            | Coronavirus                                             |                                                              |
| Hematogenous| Herpes simplex virus                                   | Enteroviruses (poliovirus, coxsackievirus, and echoviruses)    |
|            | Cytomegalovirus                                        | Cytomegalovirus                                                |
|            | Polioviruses                                           | Epstein–Barr virus                                             |
|            | Coxsackieviruses                                       | Mumps virus                                                    |
|            | Mumps virus                                            | Measles virus                                                  |
|            | Lympohocytic choriomeningitis virus                    | Adenovirus                                                     |
|            | Most arboviruses                                       | Filoviruses                                                    |
|            | Paroviruses                                            | Lymphocytic choriomeningitis virus                             |
|            | Reovirus, type 1                                       | Other arenaviruses                                             |
|            | Simian immunodeficiency virus                          | Arboviruses                                                    |
|            | Other lentoviruses and oncoviruses                     | Human immunodeficiency virus                                   |
|            |                                                          | Human T-cell lymphotropic virus                                 |

Note: ? denotes some uncertainty.
Source: Modified from Johnson RT (1998) *Viral Infections of the Nervous System*, 2nd edn. Philadelphia: Lippincott Raven.
Encephalitis, Viral

neuroinvasiveness and neurovirulence are also dependent on a myriad of host factors, such as age, immune responses, and genetic constitution.

**Acute Viral Encephalitis**

**Epidemiology**

The incidence of acute encephalitis is estimated between 3.5 and 7.4 per 100,000 persons per year (which is approximately one-third the incidence of viral meningitis). Encephalitis has been associated with approximately 100 different viruses that cause disease of variable severity (Table 3). Encephalitis is more common in children than in adults and varies by gender, season, and geographical location. For example, CNS complications of mumps virus infections are three times more common in males than females. Seasonally, enterovirus infections are more common in summer and early fall, lymphocytic choriomeningitis virus infections are more common in winter, and arbovirus infections are more common during the feeding season of the transmitting arthropod. There is marked geographical variation in the incidence and causes of viral encephalitis. For example, rabies causes more than 25,000 deaths per year in India but only 1–5 deaths in the US. Each year a variety of arboviruses cause 200–2000 cases of encephalitis in the US, tickborne encephalitis virus causes a few thousand cases in Europe, whereas Japanese encephalitis virus causes approximately 68,000 cases in Asia.

**Clinical Findings**

Clues to the causative agent may be found in a history of travel, family illnesses, recreational activities, sexual history, animal exposures, and past immunization. General examination may show a rash in enterovirus, herpesvirus 6 and 7, and West Nile virus infections; herpangina in coxsackievirus infections; adenopathy in HIV, Epstein–Barr virus, and cytomegalovirus infections; parotitis in mumps or lymphocytic choriomeningitis virus infections; or pneumonitis in adenovirus, lymphocytic choriomeningitis, or Nipah virus infections.

The classic clinical symptoms and signs of encephalitis are fever, headache, nuchal rigidity, depression of consciousness, focal neurological signs, and often seizures. Occasionally, fever is not present at the time of presentation, stupor may obscure a complaint of headache, or nuchal rigidity may be absent; thus, no finding is absolute. Spinal fluid examination is critical for diagnosis. Typically, a mononuclear cell pleocytosis, modest elevation of protein, normal glucose concentration, and often increased pressure are found. Early in disease, polymorphonuclear cells may predominate or fluid may be acellular, but within 24 h a mononuclear cell response usually evolves. In some infections, mild depressions of glucose concentration are present. The presence of red cells may suggest herpetic encephalitis, but the finding is neither consistent nor specific.

Rabies and herpes simplex virus encephalitis usually present with characteristic syndromes. Rabies may present as either an ascending paralysis simulating the Guillain–Barré syndrome or an altered mental status with periods of confusion with bizarre behavior and autonomic signs progressing to intense agitation with aerophobia and hydrophobia. Acute flaccid paralysis can also be a feature of flavivirus encephalitides, such as West Nile encephalitis, Japanese encephalitis, and tickborne encephalitis. Herpes simplex virus encephalitis usually localizes to one or both temporal lobes, which may manifest initially as subtle anoma, followed by bizarre behavior, hallucinations, aphasia, and quadratic visual field defects. Imaging studies typically show low-density lesions in one or both temporal lobes with enhancement and mass effect. Only approximately half of patients with encephalitis with temporal lobe signs prove to have herpes simplex virus encephalitis. Arboviral encephalitis, however, often causes thalamic lesions on imaging. More than 90% of patients with herpetic encephalitis have temporal lobe changes, but herpes simplex virus causes only 10% of cases of encephalitis (even fewer in some geographical regions) and other agents may occasionally mimic these symptoms and signs.

**Diagnosis**

Diagnosis of herpes simplex virus encephalitis is important because it is the most common cause of fatal nonepidemic encephalitis worldwide, and there is specific treatment that can reduce the fatality rate approximately from 70% to 20%. The second diagnostic imperative is to rule out nonviral disease that can masquerade as viral encephalitis and that requires specific therapies (Table 4). Establishing a definitive

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**Table 3** Severity of acute encephalitis with different viruses

| Virus(es)                      | Severity of encephalitis |
|-------------------------------|--------------------------|
| Rabies virus                  | >99% of cases are fatal  |
| Herpes simplex viruses        | >70% of cases are fatal (if untreated) |
| Arboviruses                   | 1–50% of cases are fatal (dependent on virus and age of host) |
| Lymphocytic choriomeningitis virus | Common mild encephalitis; rare deaths |
| Mumps virus \(^a\)             | Common mild encephalitis; rare deaths |
| Cytomegalovirus               | Occasional encephalitis with infectious mononucleosis |
| Epstein–Barr virus \(^b\)     | Occasional encephalitis with infectious mononucleosis |
| Adenoviruses                  | Rare cases of serious encephalitis in children |
| Human immunodeficiency virus  | Rare acute encephalitis at the time of primary infection |
| Human herpesvirus 6           | Mild encephalitis in children |
| Coxsackieviruses and echoviruses | Rare fatal encephalitis in neonates |

\(^a\)California encephalitis is fatal in <1% of children, western equine encephalitis in 10% of infants, St. Louis encephalitis in 20% of elderly persons, and eastern equine encephalitis in 50% of individuals of all age groups.

\(^b\)Some fatal cases have the pathology of postinfectious encephalomyelitis. Some viruses may cause acute encephalitis and acute disseminated encephalomyelitis. Source: Modified from Johnson RT (1998) Viral Infections of the Nervous System, 2nd edn. Philadelphia: Lippincott Raven.
Diagnosis can also have significant public health implications depending on the agent identified.

Diagnosis is dependent on identifying virus in spinal fluid or brain tissue or on serological tests that often require a convalescent serum too late to aid in acute management. In herpes simplex and other herpesvirus infections, polymerase chain reactions can identify specific viral DNA in spinal fluid. In many arbovirus infections, IgM-capture enzyme-linked immunoassays on spinal fluid can quickly identify specific viral infections.

### Table 4  Diseases that can masquerade as viral encephalitis

| Infectious agents | Rocky Mountain spotted fever |
|-------------------|------------------------------|
| Rickettsia         |                               |
| Bacteria           | Spirochetes                  |
|                    | Syphilis (secondary or meningovascular) |
|                    | Leptospirosis                |
|                    | *Borrelia burgdorferi* (Lyme disease) |
|                    | *Mycoplasma pneumoniae* infection |
|                    | Cat scratch fever            |
|                    | Listeriosis                  |
|                    | Brucellosis (particularly *Brucella melitensis*) |
|                    | Tuberculosis                 |
|                    | Typhoid fever                |
|                    | Whipple’s disease            |
|                    | Parameningeal infections (epidural and petrositis) |
|                    | Partially treated bacterial meningitis |
|                    | Subacute bacterial endocarditis |
|                    | Brain abscess                |
| Fungi              | Cryptococcosis               |
|                    | Coccidioidomycosis          |
|                    | Histoplasmosis              |
|                    | North American blastomycosis |
|                    | Candidiasis                 |
| Parasites          | Toxoplasmosis               |
|                    | Cysticercosis               |
|                    | Echinococcosis              |
|                    | Trichinosis                 |
|                    | Trypanosomiasis             |
|                    | *Plasmodium falciparum* infection |
|                    | *Naegleria* and *Acanthamoeba* |
| Noninfectious conditions | Glomatosis cerebi |
| Tumors             | Carcinomatous meningitis    |
|                    | Ruptured intracerebral cysts |
| Collagen           | Systemic lupus erythematosis |
| Vascular           | Rheumatoid meningitis       |
|                    | Vascultis                   |
| Other inflammatory diseases | Sarcoïdosis |
|                    | Behcet’s disease            |
|                    | Uveoncephalitis syndromes   |
|                    | Autoimmune encephalopathy   |
| Drug-induced meningitis | Non-steroidal anti-inflammatory drugs (NSAIDs) |

Source: Modified from Johnson RT (1998) *Viral Infections of the Nervous System*, 2nd edn. Philadelphia: Lippincott Raven.

### Table 5  Viruses associated with acute disseminated encephalomyelitis

| Virus(es)       | Frequency | Comment                                           |
|-----------------|-----------|--------------------------------------------------|
| Vaccinia virus* | 1:60–1:100 000 | Eliminated by discontinuation of vaccination   |
| Measles virus   | 1:1000    | Almost eliminated by introduction of vaccine     |
| Varicella–zoster virus | 1:4000 | Largely associated with acute cerebellar ataxia |
| Rubella virus   | < 1:20 000 | Reduced 99% in the US by vaccine                 |
| Epstein–Barr virus | Rare | In early weeks of infectious mononucleosis       |
| Mumps virusb   | Rare      | Reduced 99% in the US by vaccine                 |
| Influenza viruses | Rare |                                               |
| Nonspecific respiratory disease | Rare |                                               |

*Occurred with variola virus infection (smallpox), but the frequency was never accurately determined.

Although acute demyelination has been reported in a few fatal cases, mumps virus meningitis and/or encephalitis usually represent direct infection of neural cells.

Source: Modified from Johnson RT (1996) Acute encephalitis. *Clinical Infectious Diseases* 23: 219–226.

### Acute Disseminated Encephalomyelitis

#### Epidemiology

Historically, ADEM accounted for one-third of cases of acute encephalitis. Vaccine practices have reduced or eliminated the major causes (Table 5). Cessation of vaccinia infections to prevent smallpox and institution of immunizations for measles, mumps, rubella, and varicella viruses have eliminated the majority of cases of ADEM. Indeed, in nations with successful immunization policies, the majority of cases are now related to nonspecific upper respiratory infections.

#### Clinical Findings

A history is often obtained that an exanthem or a nonspecific respiratory or gastrointestinal illness preceded the encephalitis symptoms by 5 days to 3 weeks. For example, postmeasles encephalomyelitis typically begins 4–8 days after the rash when the child has defervesced and is returning to normal activities. Headache, fever, and depressed consciousness develop abruptly, often with focal neurological signs and seizures. Postvaricella encephalitis is commonly limited to acute cerebellar ataxia.

The spinal fluid may show a mild pleocytosis and protein elevation, but in one-third of patients these analyses remain normal. Assays for myelin basic protein are often positive, consistent with the demyelinating nature of the disease. Magnetic resonance imaging is the more definitive test, often showing multifocal white matter lesions with enhancement suggesting inflammatory lesions of similar age.
Diagnosis

In ADEM, virus isolation or serological studies are of little aid in diagnosis. A similar clinical–pathological syndrome follows immunization with rabies and Japanese encephalitis vaccines prepared in neural tissues and, in the case of rabies vaccines, has been shown to be associated with an immune response to myelin basic protein. Similar lymphoproliferative responses to myelin basic protein have been shown in postmeasles encephalomyelitis and in postvaricella cerebellar ataxia, indicating an analogous autoimmune mechanism. Indeed, in ADEM after measles, the virus cannot be found in the brain by virus isolation, immunocytochemical staining, or in situ hybridization; in this disease, encephalitis occurs without evidence of neuroinvasion.

Treatment and Prevention

Specific drug treatments are available only for herpesvirus infections. The incidence of HIV-associated encephalitis has been reduced by antiviral therapy, but whether this represents only a postponement of CNS disease is yet to be determined; recent data suggest that many people with HIV will progress to some form of neurocognitive deterioration. Rabies is unique in that postexposure treatment with vaccine and immune globulin can reduce the hazard of disease, but once clinical symptoms have developed, no treatment is effective. Vaccines can prevent measles, mumps, rubella, chickenpox, Japanese encephalitis, and tickborne virus infections. An additional bonus of measles immunization has been elimination vast reduction in cases of subacute sclerosing panencephalitis.

Further Reading

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