

# MENINGITIS AND ENCEPHALITIS

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*Despite the availability of effective vaccines and well-tolerated antimicrobial agents, meningitis and encephalitis remain important causes of death and neurodevelopmental complications among infants and young children. This chapter discusses the epidemiology, clinical manifestations, diagnosis, treatment, and prognosis of these disorders.*

## Meningitis

Meningitis refers to inflammation of the leptomeninges, the connective tissue layers in closest proximity to the surface of the brain. Meningitis can be caused by bacteria, viruses, parasites, and fungi, as well as by noninfectious conditions, including inflammatory disorders (eg, systemic lupus erythematosus or Kawasaki disease) and neoplasia (eg, leukemic meningitis). This chapter focuses on bacterial and viral meningitis.

### Bacterial Meningitis

#### PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Bacterial meningitis usually occurs as the consequence of hematogenous seeding of the choroid plexus, a highly vascular structure that produces cerebrospinal fluid (CSF). Less commonly, bacteria enter the CSF directly, as might occur with implantation of a bacterially contaminated ventriculoperitoneal shunt device. Because the CSF generally lacks organism-specific antibodies and complement, bacteria can grow unchecked, leading to the signs and symptoms discussed later in this chapter. Inflammatory cytokines, especially tumor necrosis factor, participate in the host responses to bacterial infection, but they also contribute to certain complications of meningitis, such as sensorineural hearing loss.

The agents causing bacterial meningitis differ substantially according to the age of the child. In the neonatal period, a relatively large group of organisms, including *Streptococcus agalactiae* (group B streptococcus), *Escherichia coli*, *Staphylococcus* species, *Listeria monocytogenes*, and *Pseudomonas aeruginosa* cause sepsis and bacterial meningitis.

*Citrobacter* species cause less than 5% of cases of neonatal meningitis but produce brain abscesses in approximately 75% of the infected infants.

In contrast, only two organisms, *Streptococcus pneumoniae*, a gram-positive diplococcus, and *Neisseria meningitidis*, a gram-negative diplococcus, currently account for most cases of bacterial meningitis among children and adolescents living in regions with compulsory immunization for *Haemophilus influenzae* type b (Hib). Prior to the development and marketing of an effective Hib vaccine, however, as many as 1 in every 400 children between the ages of 1 and 4 years experienced bacterial meningitis due to this organism.

Among unimmunized children, *H. influenzae* meningitis occurs more commonly in people with sickle cell anemia, asplenia, or human immunodeficiency virus (HIV) infection, as well as in certain populations, including African-Americans and native Americans. Risk factors for *S. pneumoniae* meningitis include many of the above variables, as well as nephrotic syndrome, cochlear implantation, and CSF leaks. College students and people with inherited complement deficiencies have an increased risk of meningitis with *N. meningitidis*. Common to many of the risk variables are immunodeficiency states that sustain bacteremia, increased exposure to the carriers of bacteria, or defects in the barriers that prevent entry of bacteria into the CSF.

#### CLINICAL MANIFESTATIONS AND DIAGNOSIS

The early signs of bacterial meningitis in the neonate can be subtle and consist only of low-grade fever, poor feeding, somnolence, “fussy” behavior, or irritability. Later, vomiting, lethargy, and seizures ensue. The physical examination

can be equally nonspecific in the young infant, demonstrating somnolence, irritability, hyperreflexia, and a full or bulging fontanelle. Meningeal signs are present infrequently. Systemic signs can include hypotension and features of disseminated intravascular coagulopathy (DIC).

The older child typically experiences signs that localize to the central nervous system (CNS), including headache, somnolence, and manifestations of meningeal irritation, the Kernig sign (involuntary spasm of the hamstring muscle provoked by knee extension with the patient supine), and the Brudzinski sign (flexion of the legs provoked by flexion of the neck). Systemic signs can include pneumonia in children with pneumococcal or *H. influenzae* meningitis and petechiae, purpura, or signs of DIC in children with meningococcal meningitis. Septic arthritis, rash, and DIC can be observed in children with *H. influenzae* meningitis.

The diagnosis of bacterial meningitis is established by lumbar puncture. The CSF in bacterial meningitis shows a neutrophilic pleocytosis, elevated protein content, and reduced glucose content. Gram stain reveals leukocytosis and the presence of bacteria, either gram-positive or -negative. The etiologic diagnosis of bacterial meningitis is confirmed by detecting specific bacterial pathogens using culture methods. Cultures can be negative when children receive oral antibiotics prior to CSF sampling, reflecting partially treated meningitis. In children with radiographic or clinical signs of increased intracranial pressure (ICP), antibiotics must be initiated empirically, and lumbar puncture should be deferred until treatment of the increased ICP.

#### TREATMENT AND PROGNOSIS

Because of the life-threatening nature of bacterial meningitis and the potential for permanent neurodevelopmental sequelae, antibiotic therapy should be instituted as soon as the diagnosis is suspected. Empiric antibiotic therapy for meningitis in infants less than 1 month of age consists of ampicillin (150–300 mg/kg/d in divided doses every 6–8 h) with gentamicin (2.5–7.5 mg/kg/d in 1–3 divided doses) or ampicillin (150–300 mg/kg/d divided every 6–8 h, depending upon the gestational and postnatal age of the infant) with cefotaxime (150–300 mg/kg/d divided every 6–8 h).

Antibiotic therapy should be modified once the identity and sensitivity profile of the pathogen have been determined. Therapy for group B streptococcal meningitis can consist of ampicillin, as above, or penicillin G 250,000 to 450,000 U/kg/d intravenously in three divided doses for infants less than 1 week old, and 450,000 U/kg/d in four divided doses for infants older than 1 week. Some infectious disease experts add gentamicin, 2.5 to 7.5 mg/kg/d in one to three divided doses. *E. coli* meningitis can be treated with ampicillin or an expanded-spectrum cephalosporin

and gentamicin, as above. *Listeria spp.* are not sensitive to cephalosporins, including the expanded-spectrum formulations, so therapy should consist of 14 to 21 days of intravenous ampicillin, 150 to 300 mg/kg/d in three to four divided doses and gentamicin, 2.5 to 7.5 mg/kg/d in one to three divided doses, depending upon the infant's gestational and postnatal age. Infants with uncomplicated cases of meningitis require 14 to 21 days of intravenous antibiotic therapy, and infants with complicated cases may require longer courses.

Empiric antibiotic therapy for suspected bacterial meningitis in children older than 1 month of age consists of vancomycin 60 mg/kg/d in four divided doses along with either cefotaxime (300 mg/kg/d in 3 or 4 divided doses) or ceftriaxone (100 mg/kg/d intravenously divided q12 h). Vancomycin, used because of potential resistance of *S. pneumoniae* to penicillin and cephalosporins, should be discontinued as soon as the causative organism is shown to be susceptible to penicillin, cefotaxime, or ceftriaxone. Resistance of *S. pneumoniae* to penicillin and cephalosporins remains a problem worldwide. Penicillin G 250,000 U/kg/d (maximum dose 12 million U/d) can be used in children or adolescents with meningococcal meningitis.

Children or adolescents with suspected meningitis require droplet and standard precautions for the first 24 hours of appropriate antibiotic therapy. Repeat lumbar puncture should be considered after 24 to 48 hours of therapy to confirm sterilization of the CSF in neonates and in children with pneumococcal meningitis who received dexamethasone or have infections with strains that are not susceptible to penicillin or cephalosporins. Infants older than 1 month of age, children, and adolescents with bacterial meningitis should receive 7 to 14 days of therapy, depending upon the organism and the response to therapy.

Despite appropriate therapy, mortality rates for infants with bacterial meningitis range from less than 10% for term infants to more than 30% for infants weighing under 1,000 g. Approximately 40% of the infants who survive neonatal meningitis have neurologic sequelae, consisting of cerebral palsy, behavioral disorders, developmental delay, hydrocephalus, and epilepsy. Stroke or cystic encephalomalacia can be detected in survivors by computed tomography (CT) or magnetic resonance imaging (MRI). Among infants older than 1 month of age, children, and adolescents the prognosis depends upon the pathogen and the presence of any underlying medical condition. Mortality rates as high as 30% can occur with pneumococcal meningitis. Sensorineural hearing loss, the most common sequela, affects 5 to 20% of the survivors; additional complications include hydrocephalus (Figure 79-1), stroke, motor disability, cognitive dysfunction, and behavioral disorders. Dexamethasone therapy, shown to reduce



**FIGURE 79-1.** Gadolinium-enhanced T<sub>1</sub>-weighted coronal magnetic resonance image in a child with *Haemophilus influenzae* meningitis shows marked basilar enhancement and enlargement of the 4th and lateral ventricles due to obstruction of the basal foramina.

the risk of sequelae in infants and children with *H. influenzae* meningitis and also in adults with meningitis, remains controversial in children with *S. pneumoniae* or *N. meningitidis* meningitis.

### Viral Meningitis

In contrast to bacterial meningitis, viral or aseptic meningitis usually represents a benign disorder with very low rates of morbidity and mortality. However, death can occur in neonates with aseptic meningitis as a consequence of hepatitis or viral myocarditis. Although many viral (Table 79-1) and some nonviral pathogens can produce aseptic meningitis, most cases result from infections with the nonpolio enteroviruses. These ribonucleic acid (RNA) viruses, comprising approximately 70 distinct serotypes, circulate among humans, and frequently cause outbreaks of disease during the summer months.

Infants with viral meningitis have fever, anorexia, vomiting, and irritability. Older children and adolescents commonly experience fever, vomiting, headache, photophobia, and signs of meningeal irritation, including the Kernig and Brudzinski signs. Systemic features at any age can include rash, myalgias, diarrhea, or signs of an upper respiratory tract illness. Hepatomegaly, congestive heart failure, or DIC

can accompany meningitis in severe neonatal viral infections, especially those due to the nonpolio enteroviruses.

The CSF in viral meningitis usually shows a mixed or lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. Gram stain may show leukocytes without bacteria. Analysis of CSF using the polymerase chain reaction (PCR) has become the gold standard for diagnosing enteroviral aseptic meningitis. PCR can also be used to detect other viral and nonviral causes of meningitis, including herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus (HHV)-6, HHV-7, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*. An etiologic diagnosis can be established in certain infections by serologic studies or by cell culture of CSF and swabbings of the oropharynx, rectum, and skin lesions.

The management of infants and children with viral meningitis consists predominantly of supportive care, including the provision of intravenous fluids and analgesia. Pleconaril, a novel antiviral agent with activity against several RNA viruses, may be of benefit in severe, life-threatening enteroviral infections, especially in infants or

**TABLE 79-1. Microbiologic Evaluation for Viruses Causing Meningitis or Encephalitis**

Pathogen	Diagnostic Method
Herpes simplex virus type 1 (HSV-1)	CSF PCR
Herpes simplex virus type 2 (HSV-2)	CSF PCR
Epstein-Barr virus (EBV)	CSF PCR; serum titers*
Varicella-zoster virus (VZV)	CSF PCR
Cytomegalovirus (CMV)	CSF PCR; culture of urine or saliva
Human herpes virus 6 (HHV-6)	CSF PCR
Human herpes virus 7 (HHV-7)	CSF PCR
Human herpes virus 8 (HHV-8)	CSF PCR
Nonpolio enteroviruses, including EV-71	CSF and serum RT-PCR; culture of stool or oropharyngeal secretions
Western and Eastern equine encephalitis viruses	Serology <sup>†</sup> ; CSF IgM
St. Louis encephalitis virus	Serology
Japanese encephalitis virus	Serology; CSF RT-PCR; CSF IgM
West Nile virus	Serology; CSF RT-PCR; CSF IgM
La Crosse virus	Serology; CSF IgM
Tick-borne encephalitis virus group	Serology
Colorado tick fever	Serology
Rabies virus	Serum titers; IFA <sup>‡</sup>

\*Acute EBV infection can be confirmed by the presence of anti-EBV viral capsid antigen (VCA) IgG /or IgM and the absence of anti-EBV nuclear antigen (EBNA) IgG.

<sup>†</sup>Agent-specific IgM and IgG in acute and convalescent serum samples.

<sup>‡</sup>Immunofluorescence antibody staining of skin from the nape of the neck. Rabies-specific antibodies can be detected after 10 days of symptoms in human rabies.

CSF = cerebrospinal fluid; IFA = immunofluorescent antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction.

immunocompromised patients. Disease-specific therapy is required for conditions, such as tuberculous, carcinomatous, fungal, or parasitic diseases, that mimic viral or aseptic meningitis.

## Encephalitis

### Epidemiology

When encephalitis was a notifiable disease in the United States, the Centers for Disease Control and Prevention (CDC) received reports of 2,000 or more cases of viral encephalitis annually, corresponding to approximately 0.5 cases per 100,000 inhabitants of the United States. Approximately 2,500 cases of HSV-1 encephalitis, a non-reportable disorder, also occur annually in the United States. During epidemics, the number of encephalitis cases can be substantially greater. More than 4,000 human cases of West Nile virus infection, an Old World flavivirus first observed in the United States in 1999, were confirmed in both 2002 and 2003. Although human rabies remains rare in most developed countries, including the United States, several thousand deaths result from rabies worldwide each year.

Information regarding residence, travel, occupational or recreational activities, and exposure to vectors provides useful clues regarding the etiology of encephalitis. Pathogens transmitted by mosquitoes or ticks, for example, typically cause encephalitis during the summer months. La Crosse virus, a mosquito-borne bunyavirus, causes summertime encephalitis in children living in the midwestern United States, whereas Japanese encephalitis, the most common arboviral encephalitis worldwide, affects people residing throughout Asia and India. *Rickettsia rickettsii*, the bacterial cause of Rocky Mountain spotted fever, a disorder that mimics viral encephalitis, causes disease from April through September in endemic regions of the U.S.

### Clinical Features and Diagnosis

The clinical manifestations of viral encephalitis include fever, headache, vomiting, altered mental status, and seizures, either partial or generalized. Partial seizures or focal neurologic deficits may indicate HSV-1 encephalitis, but focal features can also be observed in other types of viral encephalitis, including relatively benign childhood cases caused by the La Crosse virus. The neurologic examination may show hyperreflexia, ataxia, cognitive disturbances, and focal deficits, including aphasia and hemiparesis. Young infants with encephalitis often have nonspecific signs, such as inactivity, poor feeding, irritability, "fussy" behavior, and "high-pitched" cries.

The CSF in viral encephalitis usually shows an elevated protein content, normal glucose content, and a lymphocytic pleocytosis. However, the CSF findings can vary, and

in some patients, the CSF can be entirely normal. Between 5 and 15% of individuals with HSV-1 encephalitis initially lack pleocytosis (CSF cell count < 5/ $\mu$ L), a feature that complicates the diagnosis of HSV encephalitis, especially in young children. Children with CNS viral infections can have a mixed or neutrophilic pleocytosis that can resemble bacterial meningitis, especially during the early stages of viral infection. Some viruses produce mild hypoglycorrhachia, but very low CSF glucose values suggest bacterial disease rather than viral infection. Erythrocytes can be observed, particularly in HSV encephalitis, but a hemorrhagic CSF profile has little diagnostic specificity.

MRI may show unique patterns that suggest a specific pathogen. For example, children and adolescents with HSV-1 encephalitis characteristically have T<sub>2</sub> prolongation or gadolinium enhancement of the insular cortex, mesial temporal lobe, inferior frontal lobe, and cingulate gyrus. Japanese encephalitis produces abnormalities of the thalamus, basal ganglia, and brainstem. Children with acute disseminated encephalomyelitis (ADEM), an immune-mediated disorder that accounts for 15% of encephalitis cases, have multifocal areas of T<sub>2</sub> prolongation that can involve the cerebrum, cerebellum, brainstem, and spinal cord.

The electroencephalogram (EEG) should be obtained when clinicians suspect viral encephalitis; particularly when seizures complicate the illness. In patients older than 5 months with HSV-1 encephalitis, approximately 80% have focal slowing or repetitive epileptiform discharges localized to the temporal lobes. Nearly one-half of children with La Crosse virus encephalitis also have focal EEG abnormalities, indicating that the diagnosis of HSV-1 encephalitis cannot rely upon the EEG findings alone. Diffuse slowing of background rhythms or multifocal epileptiform discharges are commonly seen in children with many forms of viral or nonviral encephalitis and in ADEM.

Children with suspected viral encephalitis require a comprehensive microbiologic evaluation that reflects the season, the geographic location, and the presence of immunocompromising conditions, such as HIV infection. Numerous neurotropic viruses cause encephalitis in children (see Table 79-1). In addition, certain nonviral pathogens, such as *M. pneumoniae*, *R. rickettsii*, and *Bartonella henselae* (the cause of cat-scratch disease), as well as postinfectious conditions, including acute disseminated encephalomyelitis, mimic viral infection of the CNS.

Specimens for conventional virus isolation consist of cultures of urine, blood, CSF, feces, throat washings, and fluid from skin lesions, depending upon the suspected pathogen. Serologic studies may be the only means to confirm infections with certain pathogens, including EBV, many arboviruses, and organisms such as *M. pneumoniae* and *B. henselae*. Detecting virus-specific immunoglobulin M in CSF or serum can confirm infection with certain

arboviruses, including La Crosse, West Nile, and St. Louis encephalitis viruses.

PCR can be used to detect several viruses, including HSV-1, CMV, EBV, varicella-zoster virus (VZV), HHV-6, HHV-7, and the nonpolio enteroviruses. The sensitivity of CSF PCR in children with HSV-1 encephalitis averages 90% to 95%, but it can be as low as 70% in neonates with proven HSV disease. By combining the results of CSF PCR and MRI, the ability to detect HSV encephalitis reliably can approach 100%. Reverse transcription (RT) PCR has high sensitivity for the nonpolio enteroviruses. In contrast, the sensitivity and predictive values of PCR or RT-PCR for many other viruses are unknown, indicating that sound clinical judgment must guide the therapy of children with suspected viral encephalitis.

### Treatment

The treatment of children with viral CNS infections consists of supportive care, anticipation of potential complications, and initiation of the available specific antiviral chemotherapy. Children with encephalitis should be hospitalized and monitored closely for the development of increased ICP and seizures. Seizures affect 15 to 50% of the infants, children, or adolescents with encephalitis.

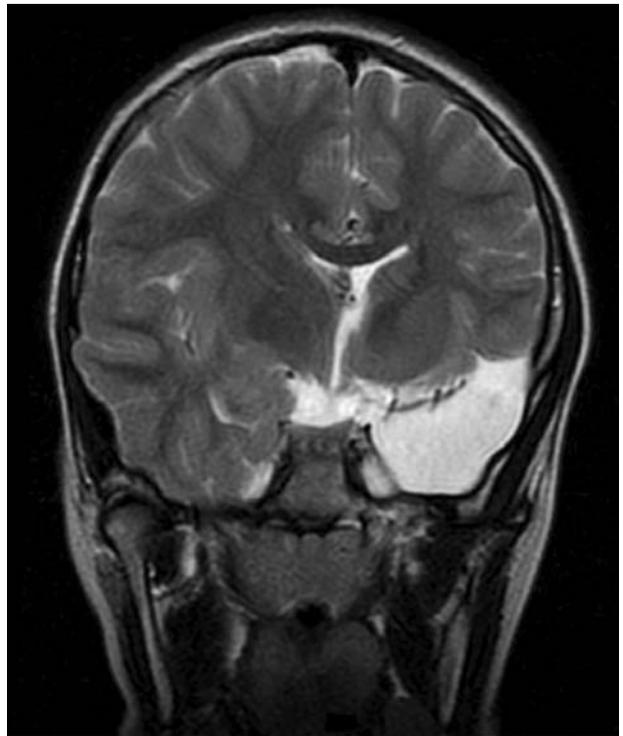
Brief or infrequent seizures can be treated with benzodiazepines (lorazepam or diazepam) using standard weight-appropriate doses (eg, 0.05 to 0.1 mg/kg of lorazepam administered intravenously; maximum single dose of 4 mg). Prolonged or repetitive seizures require loading doses of fosphenytoin, 15 to 20 mg/kg of phenytoin equivalents intravenously, or phenobarbital, 10 to 15 mg/kg intravenously in infants or toddler-aged children. Increased ICP, manifested by clinical or radiographic features, may require mannitol, hyperventilation, or placement of an extraventricular drainage catheter.

Children with suspected HSV-1 encephalitis require treatment with acyclovir, using 60 mg/kg/d divided every 8 hours. Doses of 1,500 mg/m<sup>2</sup>/d can be used in adolescents. Neonates with suspected HSV encephalitis, usually due to HSV-2, should receive 60 mg/kg/d divided every 8 hours. Dose reductions are necessary in children with impaired renal function because of the drug's potential nephrotoxicity. Patients with confirmed HSV encephalitis require therapy for 14 to 21 days (neonates with HSV encephalitis require 21 days of therapy). Complete blood cell counts should be measured twice weekly during prolonged therapy, given the potential for acyclovir-induced neutropenia. When doubt exists regarding the possibility of HSV encephalitis, full courses of acyclovir may be necessary.

Patients with encephalitis due to VZV should receive acyclovir, 30 mg/kg/d in children under 1 year of age and 1,500 mg/m<sup>2</sup>/d in older children for 10 to 14 days. Ganciclovir, using doses of 10 to 12 mg/kg/d, can be con-

sidered in patients with EBV or CMV encephalitis, but the potential side effects, nephrotoxicity, and myelotoxicity should be balanced cautiously against anticipated benefits. Children or adults with severe nonpolio enteroviral CNS infections, including disease caused by EV 71, an especially neurovirulent enterovirus, may receive benefit from pleconaril, a novel antiviral agent with activity against several RNA viruses. Anecdotal information suggests that ribavirin may have utility in West Nile or La Crosse virus encephalitis, but no controlled trials have been conducted. Patients with ADEM may respond to corticosteroid therapy.

Viral encephalitis has a variable prognosis that reflects several factors, including the etiologic agent, the patient's age, and any underlying medical conditions. Encephalitis due to the nonpolio enteroviruses and the La Crosse virus produce low rates of mortality or morbidity. Mortality in acyclovir-treated patients with HSV encephalitis currently averages less than 20%, but as many as 50% of the survivors have seizures, cognitive dysfunction, or behavioral abnormalities despite appropriate medical management (Figure 79-2). Survivors of West Nile CNS infections may also have sequelae, given the propensity of this virus to damage the brainstem and spinal cord. Human rabies encephalitis virtually always causes death.



**FIGURE 79-2.** Coronal T<sub>2</sub>-weighted magnetic resonance image in a child who survived herpes simplex virus type 1 (HSV-1) encephalitis shows complete cystic encephalomalacia of the left temporal lobe and volume loss of the left hemisphere.

## Practitioner and Patient Resources

Centers for Disease Control and Prevention. West Nile virus. Available at: <http://www.cdc.gov/ncidod/dvbid/westnile> (accessed October 8, 2004).

National Institute of Neurologic Disorders and Stroke. NINDS encephalitis and meningitis information page. Available at: [http://www.ninds.nih.gov/health\\_and\\_medical/disorders/enmenin\\_doc.htm](http://www.ninds.nih.gov/health_and_medical/disorders/enmenin_doc.htm) (accessed date October 8, 2004).

Saez-Llorens X, McCracken GH Jr. Bacterial meningitis in children. *Lancet* 2003;361(9375):2139–48.

Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002;359(9305):507–13.

### *Meningitis Foundation of America (MFA)*

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Fax: (317) 595-6370

MFA's goals are to help support sufferers of spinal meningitis and their families, provide information to educate the public and medical professionals about meningitis so that its early diagno-

sis and treatment will save lives, and help support the development of vaccines and other means of treating and/or preventing meningitis. This site provides information on symptoms, treatment, prevention, and recovery.

### *National Institute of Allergy and Infectious Diseases (NIAID)*

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<http://www.niaid.nih.gov>

NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten hundreds of millions of people worldwide. Information on allergic and infectious diseases can be found on this site.

### *The Encephalitis Society*

<http://www.encephalitis.info>

Information for families and professionals can be found at this site. The aim of the Society is to improve the quality of life of all people affected directly and indirectly by encephalitis. It fulfills this aim by supporting individuals and families of people with encephalitis and promoting better services; raising awareness among relevant professionals, statutory agencies, and the wider public about the condition and its subsequent problems; and promoting research into encephalitis.