

Viral Encephalitis

This lecture will discuss the pathogenesis, clinical manifestations, and numerous causative agents of viral encephalitis, the manifestation of viral infection of the brain parenchyma. Viral encephalitis is characterized by acute fever, headache, and evidence of parenchymal brain involvement such as changes in mental status and seizures. It can be caused by a myriad of viruses, and we will concentrate on only a few specific etiologies for the purpose of this course.

I. General Principles

A. Definitions/Distinctions

Encephalitis refers to inflammation of the brain, which should be distinguished from **meningitis**, which refers to inflammation of the meninges. Bacterial meningitis was discussed in a previous lecture.

Viral meningitis is an infection of the subarachnoid space caused by a virus. The predominant clinical features of fever, headache, and nuchal rigidity (neck stiffness), are often accompanied by nausea, vomiting, and malaise. Viral meningitis is usually a self-limited illness which lasts 7-10 days. Viral meningitis can be caused by a number of viruses, including enteroviruses (by far the most common, and discussed in the “Enteroviruses and GI viruses” lecture), arboviruses, herpesviruses, acute HIV infection, and mumps. Typical **CSF findings** in viral meningitis (see **Table I**) include a mild to moderate lymphocytic pleocytosis (elevated white blood cell count comprised mostly of lymphocytes, usually 10-500 WBCs/mm³), normal or slightly elevated protein concentration (<100 mg/dl), and a normal glucose concentration. This is in contrast to CSF findings in bacterial meningitis, which typically include neutrophilic pleocytosis (>1000 WBCs/mm³, > 80% of which are neutrophils), protein >100 mg/dl, and glucose < 40mg/dl. Note: Early during the course of viral meningitis, a neutrophilic pleocytosis may occur which evolves usually within one day to a lymphocytic pleocytosis.

Aseptic meningitis refers to the occurrence of signs, symptoms, and a CSF profile suggesting meningitis in the absence of evidence of typical bacterial, parasitic, or fungal pathogens. Viruses are the most common cause of aseptic meningitis.

Viral encephalitis refers to viral infection of the brain parenchyma. Unlike viral meningitis, which is usually benign and self-limited, viral encephalitis, depending on the specific pathogen and the host-pathogen interaction, is not infrequently associated with substantial morbidity and mortality. The symptoms include fever, headache, altered mental status, decreased level of consciousness, and focal neurological symptoms and signs which may include seizures, weakness, and speech disturbances. Typical CSF findings are similar to those found in viral meningitis (**Table I**). Refer to **Table II** for a list of viruses that can cause encephalitis. The most common causes of viral encephalitis in the U.S. are HSV-1, arboviruses, and enteroviruses.

The same viruses that produce meningitis also can produce encephalitis, but the specific viruses differ in the frequency with which they cause either syndrome. For example, HSV-2 more commonly causes meningitis than encephalitis, and HSV-1 (the most common cause of acute sporadic encephalitis in adults in the U.S.) more commonly causes encephalitis. Most arboviruses are more likely to produce encephalitis than meningitis.

Meningitis and encephalitis do not always occur exclusively. The term **meningoencephalitis** refers to inflammation of the meninges and brain parenchyma. It is important to note that the presence of altered mental status or focal neurological signs or symptoms should prompt one to consider encephalitis or meningoencephalitis, as opposed to pure meningitis, in the differential diagnosis, as this raises the possibility of different etiologies and treatment.

Myelitis refers to inflammation of the spinal cord, which can cause symptoms of weakness, paralysis, sensory loss, and bowel and bladder disturbances. Poliomyelitis (discussed in a previous lecture) is the classic example of viral myelitis, but other viral causes of a myelitis include nonpolio enteroviruses, herpesviruses, retroviruses, and West Nile virus. Meningitis, encephalitis, and myelitis may all occur together during an infection which would be accurately described as **meningoencephalomyelitis**.

Table I: Typical CSF Findings in Selected CNS infections*

Condition	Pressure (cmH ₂ O)	Cell Count (WBC/mm ³)	Cell Type	Glucose (mg/dL)	Protein (mg/dL)
Normal	9-18	0-5	Lymph	50-75	15-40
Bacterial Meningitis	20-50	100-10,000	>80% PMN	<40 (may be normal early)	100-1000
Viral meningitis/encephalitis	9-20	10-500	Lymph (early PMN)	Normal; low in LCM and mumps	50-100
TB meningitis	18-30	<500	Lymph	<50 (may be normal early)	100-300
Cryptococcal meningitis	18-30	10-200	Lymph	<40 (may be normal early)	50-300

*These represent typical findings in established disease. Overlap between the entities occurs, and the CSF profile may be different than as listed above, especially early during the course of illness or after receipt of antibiotics.

Table II. Viral causes of acute encephalitis/encephalomyelitis

Virus Family (genus)	Specific viruses
Adenoviridae	Adenovirus
Arenaviridae	LCMV (lymphocytic choriomeningitis virus), Lassa
Bunyaviridae	La Crosse, Rift Valley
Filoviridae	Ebola, Marburg
Flaviviridae	St. Louis, Murray Valley, West Nile, Japanese B, Tick-borne complex
Herpesviridae	HSV-1, HSV-2, VZV, HHV-6, EBV, CMV, Herpes B
Paramyxovirida	
(Parmyxovirus)	Mumps
(Morbillivirus)	Measles, Hendra, Nipah
Picornaviridae	Poliovirus, Coxsackie virus, Echovirus
Reoviridae	Colorado tick fever
Retroviridae	
(Lentivirus)	HIV
Rhabdoviridae	Lyssavirus, Rabies
Togaviridae	
(Alphavirus)	Eastern equine, Western equine, Venezuelan equine

B. Epidemiology of Viral Encephalitis

It is estimated that 20,000 cases of encephalitis occur annually in the U.S. The worldwide incidence is unknown, but at least 10,000 deaths due to Japanese encephalitis occur each year in Asia, and approximately 60,000 deaths due to rabies occur annually worldwide. Japanese encephalitis virus is the most common cause of viral encephalitis worldwide, and HSV-1 is the most common cause of sporadic viral encephalitis in the U.S. Specific viruses tend to occur in specific geographic and temporal niches. For example, arbovirus infections which are caused by the bite of a mosquito tend to occur in the summer in temperate climates, while HSV-1 occurs year-round. Geographic variability of the arboviruses will be discussed later. For many of the etiologic agents of viral encephalitis, infection with the virus leads most commonly to a subclinical infection, with only a small chance of the development of encephalitis. Often the chance of the development of encephalitis is greater in the very young, the elderly, and the immunocompromised. Widespread vaccination against measles and polio has decreased the occurrence of encephalitis and myelitis caused by these agents, but patients from developing countries with less successful vaccination programs, and patients from developed countries with, for whatever reason, lapses in vaccination do present with manifestations of these pathogens.

C. Pathogenesis of Viral Encephalitis

Neurotropism: the ability of a virus to infect neural cells

Neuroinvasiveness: the ability of a virus to enter the central nervous system (CNS)

Neurovirulence: the ability of a virus to cause disease of nervous tissue once it enters the CNS

Different neurotropic viruses differ dramatically in their neuroinvasiveness and neurovirulence, e.g.:

Rabies virus has high neuroinvasiveness and high neurovirulence (readily spreads to the CNS, leading to 100% mortality in the absence of early treatment).

HSV has low neuroinvasiveness but high neurovirulence (always enters the peripheral nervous system but rarely enters the central nervous system; can lead to severe consequences when it enters the CNS).

Mumps virus has high neuroinvasiveness but low neurovirulence (often invades the CNS, but neurological disease is mild).

The outcome of infection with a neurotropic virus depends on several factors including the neuroinvasiveness and neurovirulence of the virus, the site of entry and size of inoculum, and host factors including age, sex, immune status, and genetic factors. The same exposure to, e.g., St. Louis encephalitis virus could cause subclinical infection (i.e., the person is not sick) in a 25 year-old or fatal encephalitis in a 70 year-old.

Neurotropic viruses must first enter the host. **Entry** occurs via a variety of different routes, depending on the virus, including the respiratory tract (e.g., measles, VZV), the gastrointestinal tract (e.g., enteroviruses), the genitourinary tract (e.g. HIV), the skin/subcutaneous tissue (e.g., arboviruses), ocular conjunctiva (enterovirus 70), and direct inoculation into the blood (e.g., transfusion-associated HIV or CMV).

Once entry has occurred, the exact pathways used to initiate **systemic invasion** are incompletely understood but may involve adherence to M cells (specialized epithelial cells that overlie intestinal lymphoid tissue), and transport across M cells to underlying lymphoid tissue, from whence hematogenous (through the blood) or neural (through the nerves) spread can occur.

Hematogenous and **neural dissemination** are the primary mechanisms by which neurotropic viruses enter the central nervous system.

Hematogenous spread is the most common route viruses use to enter the CNS. Viruses may travel in the blood free in plasma, in association with cells, or both. The exact ways in which viruses exit the bloodstream and invade the CNS are still poorly understood. The blood-brain barrier is composed of tight junctions between brain capillary endothelial cells, and a dense basement membrane separates these cells from brain parenchyma. Breaching of this blood-brain barrier by a virus may occur via a variety of mechanisms:

1. The virus may invade the CNS at sites where the capillary endothelial cells are not joined by tight junctions and the basement membrane is thin – e.g., the choroid plexus. Infection of choroid plexus epithelial cells then leads to entry of virus into ventricular CSF and subsequently into ependymal cells lining the ventricles and the subependymal tissues.
2. The virus may directly infect cerebral capillary endothelial cells and then spread into surrounding brain tissue
3. The virus may infect and be transported within circulatory cells (including monocytes, macrophages, neutrophils, lymphocytes) which subsequently enter the CNS via diapedesis, bringing virus with them.

Neural spread is the other important mechanism by which viruses enter the CNS. Many neural cells within the CNS (including the motor neurons of the spinal cord, and olfactory neurons) have processes that extend outside the blood-brain barrier, and so axoplasmic transport within these neurons can deliver viruses directly into the CNS. Spread within neurons is the primary mode of CNS infection for rabies virus and HSV. Rabies virus enters motor neuron axons at the neuromuscular junction (where it replicates in the muscle after being inoculated via a bite) and is transported retrograde directly into the CNS. As discussed in a previous lecture, HSV achieves latency in the dorsal root ganglia. Upon reactivation, it can be neurally transported anterograde to the skin leading to vesicular skin lesions, or it can be transported retrograde to the CNS and cause encephalitis. Neurotropic viruses which enter the host via the gastrointestinal tract (e.g. poliovirus) can infect neurons in the myenteric plexus and be transported to the CNS via the vagus nerve. Invasion of the CNS through olfactory nerves in the nasal mucosa has been documented in experimental animals, but its role in the development of naturally occurring human disease is not established for viruses.

Neurovirulence: Once inside the CNS, many neurotropic viruses infect the neurons, and the outcome of infection can be latency (the cell has little or no change in its morphology or function), subtly altered cellular functions, or cell death via apoptosis or necrosis. Cell death via necrosis involves early disruption of the cytoplasmic membrane integrity with subsequent release of intracellular proteins and an inflammatory response. Clinical manifestations of the neuronal death or dysfunction depend in part on the anatomic location (cortical infection leading to change in neurocognitive functioning; brainstem infection leading to coma and respiratory failure). Less commonly, oligodendroglial cells may be infected, as in JC virus infection which, when reactivated in immunosuppressed individuals, leads to demyelination and the aptly named syndrome of progressive multifocal leukoencephalopathy (PML).

Immunopathology: As with many viral infections, a substantial proportion of the pathology may actually be caused by the host immune response to the viral infection. During severe encephalitis, an inflammatory reaction is usually prominent in the meninges and in a perivascular distribution within the brain. To what degree this plays a protective (clearing virus and virally infected cells) vs. pathologic (release of pro-inflammatory cytokines which contributes to neuronal dysfunction and death) role is unclear.

So far we have been discussing encephalitis that results from direct invasion of the brain parenchyma with viruses. However, the brain (as well as the spinal cord and peripheral nerves) can also be affected by postinfectious demyelinating processes that do not necessarily involve direct invasion of the brain with the etiologic agent. **Acute disseminated encephalomyelitis (ADEM)** is an illness of the CNS in which demyelination occurs after infection with a virus, usually following the systemic illness by days to weeks. The clinical manifestations can be difficult to differentiate from encephalitis caused by direct invasion of the virus. The pathogenesis of this syndrome is thought to be related to induction of an immune response to CNS myelin. Systemic infection with measles, varicella, and influenza A, to name a few, have been associated with a postviral encephalomyelitis.

D. Clinical Findings in Viral Encephalitis

Cardinal signs and symptoms of encephalitis include headache, fever, alterations of consciousness (ranging from lethargy to coma), confusion, cognitive impairment, personality changes, motor weakness, seizures, movement disorders, accentuated deep tendon reflexes, and extensor plantar responses. Increased intracranial pressure can occur, manifested by papilledema, cranial nerve palsies, and progression to coma. Viral encephalitis is usually an acute illness, with or without a prodrome, but can also be a slowly progressive disease as in progressive multifocal leukoencephalopathy (PML) caused by JC virus, subacute sclerosing panencephalitis (SSPE) occurring after measles, and HIV encephalopathy.

E. Diagnosis of Viral Encephalitis

Diagnosis begins with a thorough and detailed history which seeks to identify exposures by inquiring about insect or animal bites, recent travel, sexual exposures, and immunization status. Physical examination should look for signs of systemic illness such as rashes or lymphadenopathy (enlarged lymph nodes) as well as evidence of meningismus (stiff neck), decreased level of consciousness, or focal neurologic signs such as weakness, speech abnormalities, increased tone, and plantar extensor reflexes. The most important laboratory evaluation is the CSF profile, the major characteristics of which have been discussed above. Appearance of red blood cells (RBCs) in CSF may occur in HSV encephalitis. Bacterial, fungal, parasitic, or treponemal (specifically syphilis) causes should be ruled out with appropriate stains, cultures, and antigen tests of CSF. Search for specific viral etiologies can occur with cultures (of CSF or other fluids), serology (CSF and serum) and detection (in CSF > serum) of viral nucleic acid by PCR, depending on the specific etiology considered. Neuroimaging findings are often nonspecific. CT scans are often performed to establish the safety of performing lumbar puncture when elevated intracranial pressure is suspected or, when given with contrast, to rule out other causes such as brain abscess. MRI, however, which is more sensitive than CT, may reveal focal areas of edema or enhancement, and should be performed early during the evaluation. The electroencephalogram (EEG) is often abnormal in acute viral encephalitis, with diffuse slowing, but certain patterns may suggest specific diagnoses (such as HSV, SSPE).

F. Treatment of Viral Encephalitis

Treatment is often supportive, involving management of increased intracranial pressure, treatment of seizures, and management of metabolic derangements. **The most important point to make about treatment, however, is that HSV encephalitis responds to treatment with intravenous acyclovir.** Because this is a relatively well-tolerated treatment, most patients presenting with a syndrome consistent with encephalitis are treated empirically with acyclovir for the possibility of HSV encephalitis, until HSV encephalitis is ruled out or another etiology is confirmed.

II. Specific Examples

A. HSV Encephalitis

Clinical Vignette

A 50 year-old previously healthy man who lives in Riverdale awakens from a nap that he was uncharacteristically taking on a Saturday afternoon in December, puts on his swimsuit, and begins to fill the bathtub with shredded pieces of that day's newspaper. Although he doesn't find anything odd about his behavior, he does complain of a headache which allows his wife to convince him to go the E.R., where he is found to have a temperature of 102.4 and extreme lethargy.

Epidemiology:

HSV epidemiology, pathogenesis, and clinical features were discussed extensively in a previous lecture. However, HSV encephalitis must be briefly highlighted here because it is the major treatable viral encephalitis. It is also the most common cause in the U.S. of sporadic, fatal encephalitis, with 1000 to 2000 cases occurring annually in the U.S. It is nearly always (96%) caused by HSV-1. HSV-2 more typically produces aseptic meningitis but may cause encephalitis in neonates with disseminated disease, when spread to the CNS may be hematogenous. HSV encephalitis occurs in children and adults year-round.

Pathogenesis:

Proposed entry into the CNS involves retrograde transport of virus via olfactory or trigeminal nerves. In the CNS it replicates in both neurons and glia, causing necrotizing encephalitis and widespread hemorrhagic necrosis throughout the brain parenchyma, but particularly the temporal lobe. HSV encephalitis can occur as a result of reactivation from latency (1/2 - 2/3) or during primary infection (1/3 - 1/2). It is more commonly associated with reactivation in older patients, and primary infection in the younger population.

Clinical features:

Clinical manifestations of HSV encephalitis include fever, headache, altered consciousness (i.e., lethargy to coma), disorientation, personality changes, focal weakness, altered speech, cranial nerve abnormalities, and seizures. The personality changes and bizarre behavior specifically are suggestive of HSV encephalitis and are thought to be due to temporal lobe involvement. Onset is usually sudden without a prodrome. Characteristic CSF findings are as previously discussed for viral encephalitis, but the presence of red blood cells in the CSF, indicative of the hemorrhagic nature of this encephalitis, is suggestive, but not diagnostic, of HSV encephalitis. MRI, which

may be normal early in the course, may reveal temporal lobe edema or enhancement, hemorrhage, or mass effect. EEG may reveal abnormalities specifically localized to the temporal lobe.

Diagnosis:

Diagnosis is made by detecting HSV nucleic acid via PCR of CSF, which is highly sensitive (98%) and specific (94%), and has replaced brain biopsy as the “gold standard” for diagnosis. HSV is successfully isolated by culture of CSF in less than 2% of cases. Serology is of limited role, particularly as at least one-half of patients with HSV encephalitis have recurrent infections and, therefore, preexisting antibody responses.

Treatment:

Treatment with intravenous acyclovir should be initiated as soon as possible, and continued for 14 to 21 days if the diagnosis of HSV encephalitis is confirmed and perhaps in the absence of a confirmed diagnosis of HSV encephalitis if no other diagnosis is confirmed or likely. Early treatment with acyclovir reduces mortality from 70% to 19%, but even with treatment 62% of survivors have moderate to severe residual neurologic sequelae. Of note, empirical acyclovir therapy does not appear to decrease the ability to diagnose HSV encephalitis via PCR for the first 24 to 48 hours. Patients older than 30 years and those with duration of symptoms greater than 4 days before initiation of treatment have worse prognoses.

B. Arboviral Encephalitis

Definitions/examples:

The term arbovirus (**arthropod-borne virus**) refers to viruses that are transmitted to humans by biting insects (mainly mosquitoes and ticks). The term “arbovirus” is not used for taxonomic purposes. There are more than 500 “arboviruses” which come from several different virus families. Arboviruses are maintained in nature via a transmission cycle between primary, nonhuman animal hosts (often birds) and arthropod vectors, and they can be transmitted incidentally to humans by arthropod vectors. The virus usually causes a prolonged and asymptomatic viremia in its primary host, but a brief and low-level viremia in its incidental/accidental host (human or domestic animal) which usually serves as a “dead end host” because the low-level viremia does not support secondary transmission. Most human infections with arboviruses are asymptomatic. When disease is produced, clinical illness is usually self-limited, but can be severe or even fatal.

The arboviruses include important etiologic agents of meningoencephalitis. However, as way of introduction, the arboviruses can also cause a huge variety of systemic diseases which will not be discussed further during this lecture but which include Yellow fever virus (a flavivirus transmitted by mosquitoes in South America and Africa which causes jaundice and hemorrhages), and Dengue virus (a flavivirus transmitted by mosquitoes in the Caribbean, Southeast Asia and China which causes “breakbone fever” and hemorrhagic fever).

The three main virus families which account for the arboviruses causing encephalitis, along with a few select examples of specific viruses, are shown below:

Virus family (genus)	Virus properties	Examples
Togaviridae (Alphavirus)	ssRNA, (+) enveloped	Eastern equine encephalitis Western equine encephalitis
Flaviviridae (Flavivirus)	ssRNA, (+) enveloped	Japanese encephalitis St. Louis encephalitis West Nile
Bunyaviridae (Bunyavirus)	ssRNA, (-) segmented, enveloped	California serogroup, including LaCrosse virus

Epidemiology:

In terms of numbers, the most important member of the group is Japanese encephalitis virus, which causes an estimated 50,000 cases of encephalitis and 10,000 deaths in Asia every year, affecting mostly children. In contrast, St. Louis encephalitis virus causes a median of 135 annual cases of encephalitis in the U.S., but transmission in the eastern U.S. usually occurs in localized and regional outbreaks. Prior to 1999, there were four numerically important arboviral causes of encephalitis in the U.S. In 1999, West Nile, which will be discussed later, joined the list. First we will discuss the other four, which include Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis, and LaCrosse (California serogroup) encephalitis. These arboviruses have been the cause of many outbreaks of encephalitis in the U.S.

Pathogenesis:

The pathogenesis is similar to that of viral encephalitis in general. Features specific to the arboviruses include mode of transmission which is from bite from infected vector, replication in local tissues, viremia, and hematogenous invasion of the CNS. The neuron is the primary target in the CNS and CNS disease is mostly due to neuronal dysfunction and neuronal death induced directly by the virus. The age of the host is of paramount importance in determining neuroinvasiveness and neurovirulence.

Clinical features:

The spectrum of illness caused by these four agents ranges from clinically inapparent, to fever and headache, to aseptic meningitis, and finally to encephalitis. The incubation period (the period from presumed contact until the onset of the clinical illness) is 4-10 days. They are all transmitted by mosquitoes, and so illness is seen during mosquito season (late spring to early fall). When encephalitis occurs, the viral agent often cannot be determined based on clinical symptoms, and diagnosis depends on attention to epidemiologic features such as age and geography as well as laboratory diagnosis. The clinical manifestations of arboviral encephalitis include the fairly acute onset of fever, nausea, vomiting, and headache, followed within 24 hours by confusion and disorientation. The mental status changes range from subtle changes detected only by specific neurocognitive testing to severe disorientation and coma. Cranial nerve abnormalities, weakness, and tremor may occur, along with rash, myalgias, and photophobia. In infants, the only manifestation may be fever and seizures.

Diagnosis:

Diagnosis is made by isolating the virus or detecting viral antigen or nucleic acid in the CSF, or detecting an immune response to the individual agent via acute and convalescent serology.

Treatment:

Treatment is supportive, as specific antiviral agents are not available. Neurologic sequelae can include cognitive impairment, personality changes, seizures, blindness and deafness.

Prevention:

Vaccines are not currently available for the arboviruses for use in humans except for an inactivated Japanese encephalitis vaccine. Prevention involves decreasing contact between humans and potentially infected vectors (see below under West Nile virus)

Specific arboviral agents:

Eastern equine encephalitis virus and **Western equine encephalitis virus** are both alphaviruses. Their transmission cycles involve swamp-dwelling birds and mosquitoes, with horses and humans as accidental dead-end hosts. They were both first isolated in the 1930's from the brain tissue of horses during outbreaks of equine encephalitis (EEE in New Jersey; WEE in California), and both cause outbreaks of encephalitis in humans in summer/early fall which may be preceded by epizootics in horses. EEE virus has been isolated along the east coast of North America and South America. Infants, children, and adults over 55 years of age are most often affected, and males and females are equally affected. An infected human is 25 times more likely to experience inapparent infection than clinical illness, and the spectrum of illness ranges from mild to fatal. Mortality rate among those with encephalitis can exceed 50%. Unlike other causes of viral encephalitis, EEE not infrequently causes a cloudy CSF with >1000 WBCs. Western equine encephalitis virus, also an alphavirus, occurs everywhere in the U.S., but especially the Central Valley of California, and also in Canada and Brazil. Highest attack rates occur in adults over 55 years of age, and the case fatality rate is 5-10%.

St. Louis encephalitis virus is a flavivirus which caused a major outbreak of human encephalitis in St. Louis in 1933. Its transmission cycle also involves birds and mosquitoes, and it has caused encephalitis in all areas of the U.S. in midsummer/early fall, and also occurs in the Caribbean and Central and South America. Infection rates are similar in all age groups, but chance of developing clinical encephalitis increases with age. Of those with clinical illness, 75% have encephalitis. Dysuria and urinary frequency also occur in 20%. Mortality in outbreaks ranges from 2-12%, but case fatality rate in the elderly can be 30%.

LaCrosse virus is the most prevalent virus in the **California group of bunyaviruses**. Its transmission cycle involves chipmunks/squirrels and mosquitoes, and it occurs mostly in the Midwestern U.S., but also Texas and the east coast. It causes encephalitis mostly in rural areas, among 5-10 year-olds, and boys are affected more than girls. The case fatality rate is <2%, but 1/3 of affected persons have abnormal neurologic findings at discharge. It can cause temporal lobe abnormalities on MRI and EEG.

C. West Nile Virus

Clinical Vignette

A 66 year old man from Staten Island experiences the onset, in June, of fever, chills, headache, nausea, vomiting, muscle aches, fatigue, muscle weakness, dizziness, decreased appetite and chest pain. After more than two weeks of low-grade fevers, he has abrupt onset of double vision and mental status changes, and is admitted to the hospital.

Epidemiology/History:

West Nile virus was recognized in the United States for the first time in 1999, when it caused an epidemic of meningoencephalitis associated with muscle weakness in New York City. Initial investigations suggested that St. Louis encephalitis virus was the cause, as the first 8 patients tested positive for antibodies against SLE due to cross-reactivity with this flavivirus. However, at the same time, an unusual number of deaths were observed in birds, mostly crows, and in some exotic captive bird species in the Bronx Zoo, and SLE usually does not cause deaths in birds. Eventually, the National Veterinary Services Laboratories in Ames, Iowa, isolated a virus from the birds' tissues. Subsequent testing performed at the CDC and the University of California at Irvine revealed that this virus was closely related to West Nile virus, and that it was identical to virus from human brain tissue from 4 of the human encephalitis cases in NY. On retesting of patient samples, all initial serum and CSF specimens reactive to SLE were positive for WNV by IgM ELISA. Furthermore, an additional 18 patient samples that had been negative or borderline for SLE were positive for antibody to WNV.

The West Nile virus had not previously been identified in the U.S. It had been known to cause flulike illness as well as outbreaks of meningoencephalitis in Israel, Africa, Romania and Russia. Since the first occurrence in the U.S. in 1999, West Nile virus had steadily spread westward among several species of birds and mosquitoes, and had caused increasing numbers of illness in humans. In 1999, only New York state was involved, and 62 cases and 7 deaths were reported. By the end of 2004, West Nile virus had been found in all states except Alaska and Hawaii. The 2002 and 2003 West Nile virus outbreaks, which involved 2942 and 2866 cases of meningitis or encephalitis, and 284 and 264 deaths, respectively, represented the largest-ever outbreaks of arboviral encephalitis in North America. However, between 2004 and 2007 the number of cases of meningitis, encephalitis, and death was substantially lower. In 2006 and 2007 there were 1459 and 1217 cases of meningitis or encephalitis, and 177 and 124 deaths, respectively.

West Nile virus infection of humans most commonly occurs through the bite of an infected *Culex* mosquito, and so people at risk of exposure include those spending time outside when mosquitoes are actively biting. Risk of infection occurs during the adult mosquito season (June through October). The mosquito becomes infected when feeding on infected, highly viremic birds. Crows and blue jays in particular are highly susceptible to West Nile virus. Humans, horses, and most other mammals are traditionally thought of as dead-end hosts because they do not develop high-level viremia to allow subsequent transmission to others via mosquito bite. However, the following 4 new modes of transmission which were recognized in 2002 suggest at least some degree of sustained viremia: organ transplantation, breast-feeding, blood transfusion, and transplacental transmission.

Most human infections are clinically inapparent. Serologic epidemiologic studies suggest that 1 in 5 infected persons will experience a brief febrile illness. Approximately 1 in 150 infected persons will experience a severe illness with CNS involvement, and risk is greatest for the elderly. People older than 50 years have a 10-fold higher risk of developing neurologic symptoms, and this increased risk increases to 40-fold in patients older than 80 years.

Pathology:

The West Nile virus is a flavivirus and, like St. Louis encephalitis virus, is a member of the Japanese encephalitis virus serocomplex. It is an enveloped single-stranded RNA virus which has 2 important glycoproteins – M (membrane) and E (viral envelope). The E-glycoprotein mediates virus-host cell binding and elicits most of the virus-neutralizing antibodies. The exact mechanism by which CNS infection occurs is uncertain, but seems likely to involve endothelial replication and subsequent crossing of the blood-brain barrier, or axonal transport through olfactory neurons. The increased risk in the elderly may be due to immune dysfunction leading to prolonged or greater viremia, or due to disruption of the blood-brain barrier.

Clinical features:

The incubation period of West Nile is 2-15 days. As discussed above, most persons with clinical illness will experience a brief (3-5 days) illness involving fever, headache, and myalgias, and quick and full recovery. Generalized lymphadenopathy and a maculopapular rash involving face and trunk are common. In patients in whom neurologic illness occurs, meningoencephalitis is the most common type, although isolated encephalitis or meningitis may also occur. One of the notable features of West Nile meningoencephalitis has been an acute flaccid paralysis syndrome resembling poliomyelitis. This involves asymmetric weakness and decreased deep tendon reflexes, with no sensory involvement, and, like polio, involves localized damage to anterior horn cells of the spinal cord. Other features may include seizures, cranial nerve abnormalities, ataxia, and movement disorders including tremors, myoclonus, and parkinsonism. CSF findings include mild lymphocytic pleocytosis, mild to moderate protein elevation, and normal glucose. MRI may reveal leptomeningeal or periventricular enhancement, or involvement of the thalamus and basal ganglia. West Nile meningoencephalitis has been associated with up to 10% mortality and long-term morbidity including continuing neurologic abnormalities, fatigue, and headaches.

Diagnosis:

The most sensitive screening test for West Nile virus is the IgM-capture enzyme linked immunosorbent assay (ELISA) for CSF and/or serum. (Note, however, that cross-reactivity with SLE virus and other flaviviruses can occur, and positive results by ELISA should be confirmed with a more specific test called the plaque reduction neutralization test.) The West Nile IgM antibody usually persists for more than 6 months after illness, and so its presence should suggest acute infection only in the context of a compatible illness. Viral RNA can also be detected via PCR in CSF and serum, but this is considerably less sensitive than the IgM antibody. Virus isolation is usually unsuccessful because of low level and short duration of viremia. **The New York State Department of Health performs a PCR panel on CSF of patients hospitalized with viral encephalitis which includes arboviruses, enteroviruses, herpes simplex virus, cytomegalovirus, varicella zoster virus and Epstein-Barr virus.**

Treatment: There is currently no specific therapy proven to be effective for treating West Nile viral encephalitis, although interferon alpha, ribavirin, and immunoglobulin have been tried anecdotally and are currently being evaluated in clinical trials

Prevention:

Currently prevention includes limiting contact between humans and potentially infected mosquitoes. Personal protective measures include avoiding outdoor activity from dusk to dawn (peak mosquito feeding times), use of DEET-containing insect repellent (or repellent containing picaridin or oil of lemon eucalyptus) on skin and clothing, wearing long-sleeved shirts and pants while outside, maintaining window screens, and eliminating standing water which can serve as breeding ground for mosquitoes. Government-run mosquito control programs include application of larvicides to water collections and pesticide spraying for adult mosquito control. Vaccines against West Nile virus are under evaluation.

D. Rabies

Rabies has been inciting terror among humans for at least 4000 years, due to the inexorable death that follows the development of symptoms, and it remains a modern problem in much of the developing world and in the U.S., where the disease is enzootic in bats and wild mammals. The term *rabies* may be derived from the Sanskrit *rabhas* (“to rage”) or the Latin *rabere* (“to rave”). Rabies virus was first isolated by Pasteur in the 1880’s. Rabies viruses are members of the *Lyssavirus* genus of the rhabdoviridae family of viruses which is comprised of two genera: *Vesiculovirus* and *Lyssavirus* (from the Greek *lyssa*, “frenzy”). They are enveloped, bullet shaped viruses with non-segmented negative-strand RNA genomes of about 11,000 nucleotides that code for 5 proteins (L, P, N, M, and G). Although it was previously believed that a single virus type was responsible for all rabies, modern techniques have shown that several viruses and at least 6 serotypes in the *Lyssavirus* genus cause diseases clinically related to rabies.

Epidemiology:

An estimated 60,000 human fatalities due to rabies occur yearly worldwide. Rabies has a worldwide distribution, although a handful (mostly island) nations (including the United Kingdom, Japan, Taiwan, New Zealand, Spain, Sweden and Norway) and Hawaii remain rabies free at this time. The major foci of rabies in the world are the Indian subcontinent, Southeast Asia, and most of Africa. Rabies is transmitted primarily by the bite of an infected animal although inhalation and transplants have also been implicated. (In June, 2004, four people died from rabies after receiving organ transplants in Texas from a 20 year-old donor with unrecognized rabies infection.) In developed countries, 90% of human exposures are due to wild animals (skunks, raccoons, foxes, and bats being the most prominent), and 10% are due to domesticated animals (dogs, cats, cattle). In developing countries, dogs are the most common cause. Rabies can infect any mammal although active infections of small mammals (e.g. squirrels, rabbits, rats) are uncommon as they are usually killed by attacks from rabid animals.

The incidence of rabies in humans in the U.S. decreased dramatically with the introduction of community-wide rabies immunization for domestic animals. In the U.S., 1 to 3 fatal human cases per year have occurred during the past 20 years. Anyone who is bitten by a wild animal anywhere in the U.S. should be considered at risk for rabies infection. Bats are now the major source of human rabies in the U.S, and for many patients in whom viral analysis shows that the rabies virus strain is of bat origin, no history of an actual bite can be obtained. The CDC recommends postexposure rabies prophylaxis (see below) for anyone who has contact with a bat,

even if there has been no bite, and this would include any person who awakens from sleep and finds a bat in the room.

Pathogenesis:

Initial infection in the host requires interaction of the surface glycoprotein, G, with a cellular receptor. Replication requires active, ongoing translation and the wrapping of template RNA by the N protein as it is synthesized. Actual transcription occurs in the cytoplasm. The positive strand RNA that is produced serves as the template for the daughter negative strand genomic RNA. The RNA polymerase (L protein) has a high misincorporation rate and does not have a proofreading function. This allows virus to mutate quickly. The virus particles are assembled and then bud from the plasma membrane as the M protein interacts with the cytoplasmic tail of the surface protein, G. Once inside the host, the virus does not need to be enveloped nor does it require its surface glycoproteins (M and G) to spread within the nervous system. Strains vary in G protein expression and there seems to be an inverse correlation between G levels and *in vivo* pathogenicity.

Rabies infection involves centripetal spread of the virus via the peripheral nerves to the central nervous system. Usually, rabies is transmitted by saliva from infected animal bites but may also be transmitted by scratches, secretions that contaminate mucous membranes, aerosolized virus that enters the respiratory tract, and corneal and solid organ transplants. After entering through a break in the skin, across a mucosal surface or through the respiratory tract, virus replicates in muscle cells and in doing so infects the muscle spindle. It then infects the nerve that innervates the spindle and moves centrally within the axons of those neurons. Replication occurs in peripheral neurons but not usually in glia. After reaching the spinal cord, the virus spreads throughout the CNS, causing neuronal degeneration. After CNS infection the virus spreads to the rest of the body via the peripheral nerves. The high concentration of virus in saliva results from viral shedding from sensory nerve endings in the oral mucosa as well as replication within the salivary glands. Within the brain, despite the extensive CNS functional impairment, little histopathologic change can be observed in the affected tissue other than the presence of Negri bodies, which are cytoplasmic inclusions containing considerable amounts of viral antigen.

Clinical features:

The incubation period ranges from 1 week to 1 year, although the average incubation period is 1-2 months. The length of time from inoculation to clinical disease is determined by the distance between the inoculation site and the brain (longer distance, longer incubation; facial bites are particularly dangerous). The disease exhibits a 100% fatality rate once clinical symptoms manifest in an unvaccinated individual (except for one case report cited below). Even in individuals who received preexposure or postexposure prophylaxis before the onset of clinical disease, only 6 documented cases exist of survival after onset of clinical rabies. The classic presentation is a 1 day to 2 week febrile prodrome, often with paresthesias, pain or numbness at the site of the bite, followed by anxiety, agitation, delirium, hypersalivation/drooling, and spasm of the pharyngeal muscles at the sound, sight, or taste of water (hydrophobia). Seven to 10 days after the onset of the neurologic symptoms, generalized flaccid paralysis, seizures, and coma ensue, with ultimate respiratory and vascular collapse. Alternatively and less commonly, rabies may present as pure ascending paralysis without sensory involvement.

Diagnosis:

Diagnosis can be made before death by isolation of the virus or detection of nucleic acid from patient saliva, demonstration of viral antigen in the highly innervated hair follicles obtained by biopsies along the hairline of the neck, detection of viral antigen in touch impressions from the cornea, or the presence of antirabies antibodies in the serum or CSF of unvaccinated patients. Postmortem diagnosis is made by the finding of characteristic inclusion bodies in the brain (Negri bodies), RT-PCR of brain, and/or immunohistochemistry.

Treatment/Prevention:

The classic teaching regarding the prognosis of rabies is that **once clinical symptoms arise in an unvaccinated individual there is no effective treatment.** However, in 2004, a 15-year-old girl from Wisconsin, who developed rabies after a bat bite and received no vaccination, survived after treatment involving induction of therapeutic coma, and anti-excitatory and antiviral drug therapy. It remains unclear if her survival was due to an attenuated variant of the virus or a rare host polymorphism (NEJM 2005; 352:2508-14). Thus whether such treatment will be successful in subsequent cases has yet to be determined.

Rabies may be prevented by both pre and post-exposure prophylaxis (in addition to efforts to decrease exposure to rabid animals). **Pre-exposure prophylaxis** consists of three doses of rabies vaccine and is recommended for veterinarians and some travelers to highly-endemic rural areas. Booster doses are recommended every two years and after any exposure. **Post-exposure prophylaxis** consists of first cleaning the bite site thoroughly and then providing rabies immune globulin (passive vaccination) and rabies vaccine (active vaccination) as soon as possible. The goal of post-exposure prophylaxis is to ensure the presence of a rabies-specific immune response in the exposed individual before rabies virus can replicate in the central nervous system. Because of the relatively long potential latency period of rabies, post-exposure prophylaxis should be considered for high risk exposures even if months have passed since the event. In the U.S., every bite by a wild animal must be considered potentially rabid, as should bites from any dog, domestic or wild, in developing countries, where immunization of domestic animals may not be current. Bites from reliably immunized domestic animals that are available for observation may be managed expectantly. If the animal is well after 10 days no treatment is necessary. If the animal sickens or dies, post-exposure prophylaxis should be started and continued until the animal's brain tests negative for rabies.

The rabies immune globulin is administered in a single dose. As much of the dose as possible should be injected directly into and around the wound.

The original rabies vaccine was developed by Pasteur who dried the spinal cord of a rabid rabbit in the sun (UV inactivation). This vaccine was very efficacious but was replaced because the injection of CNS material precipitated experimental allergic encephalitis which resembled multiple sclerosis. Three vaccines for human use are approved in the U.S., all of which are inactivated virus vaccines. The preferred vaccine, because of its safety and tolerability profile, is the human diploid cell vaccine (HDCV). The vaccination series consists of five doses administered in the deltoid area on days 0, 3, 7, 14, and 28.