Emerging Viral Infections of the Central Nervous System

Part 2

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One of the more dramatic examples of viruses and associated diseases spreading to new niches is JC virus–associated PML. Progressive multifocal leukoencephalopathy is a demyelinating disease of the CNS caused by the polyomavirus “JC” that occurs almost exclusively in immunocompromised individuals, particularly those with depressed cell-mediated immunity. Infection with JC virus is widespread in the general population, with more than 80% being seropositive by adulthood. Following primary infection, virus becomes latent in a variety of tissues including kidney, tonsils, lymphoid organs, and bone marrow. Depression in cell-mediated immunity is presumed to result in viral reactivation with subsequent dissemination from extraneural sites to the CNS through the bloodstream, leading to lytic infection of oligodendrocytes and resulting demyelination. Recent studies raise the alternative possibility that following initial infection virus may become latent in the CNS and might therefore reactivate directly in that site to produce disease. Regardless of the pathogenetic mechanism, PML appears to result exclusively from viral reactivation rather than primary infection. The disease develops despite a typically brisk antibody response in serum and CSF, suggesting that antibody has a relatively limited role in prevention of reactivation or control of infection. As noted, patients with PML typically have defects in cell-mediated immunity. Recent studies suggest that CD8+ T cells directed against epitopes on the viral capsid protein VP1 may play a particularly important role in disease control and prevention, and the presence or lack of these cells predicts risk of disease and correlates with outcome.

With the advent of the human immunodeficiency virus (HIV) pandemic, HIV infection became the most significant risk factor for PML, accounting in some series for up to 80% of total cases. With the advent of highly active antiretroviral therapy (HAART), the incidence rates for PML in HIV-infected treated individuals have declined substantially. A recent large Dutch population-based cohort study found that the incidence of PML in HIV-infected individuals had declined from 3.3 cases per 1000 person-years at risk (PYR) in 1995-1996 (pre-HAART) to 1.3 cases per 1000 PYR in the 2000-2006 period (HAART era). The rate was even lower among patients known to be receiving...
The absolute CD4 T-cell count was a major influence on risk of developing PML, with the incidence rate being nearly 50-fold higher in those with CD4 cell counts less than 200/mm³ (9.1 per 1000 PYR) as compared with those with counts more than 200/mm³ (0.2 per 1000 PYR). As the use of immunomodulatory therapy for antirejection regimens and for treatment of autoimmune diseases has increased, the settings in which PML has been reported have also expanded. In 2005, 3 cases of PML were reported in patients receiving the humanized monoclonal antibody natalizumab (Tysabri) for treatment of multiple sclerosis (2 cases) or Crohn disease (1 case) (Figure 1).

A subsequent analysis suggested that the risk was approximately 1 PML case per 1000 treated patients per 18 months of therapy. The initial cases had received other immunomodulatory drugs, including interferon beta-1a, and it was initially suggested that these might influence the risk. Natalizumab was initially withdrawn from the market and then reintroduced in July 2006 for use as monotherapy. Since the reintroduction of natalizumab, 9 additional cases of PML in patients with multiple sclerosis receiving natalizumab monotherapy have been reported by Biogen Idec. These cases had received treatment for between 12 and 35 months. The company reported that as of the end of March 2009 about 40,000 patients were receiving Tysabri monotherapy, including about 20,800 in the United States. Of the total group, approximately 24,900 patients had received more than 12 months of monotherapy; 14,400, more than 18 months; and 6,800, more than 24 months. These numbers suggest that the risk of natalizumab-induced PML in patients with multiple sclerosis is likely similar to or less than originally projected following the initial reports.

Natalizumab is a monoclonal antibody directed against α₄ integrins and inhibits binding of lymphocytes and other cells expressing αβ₅ or αβ₇ integrin to endothelial cells expressing the ligands for these molecules, including vascular cell adhesion molecule 1 and fibronectin, or to mucosal cells expressing mucosal addressin cell adhesion molecule 1. It has been suggested that the inhibition of lymphocyte trafficking into the CNS, which is central to the proposed therapeutic mechanism of action of natalizumab in MS, also prevented entry of JC virus–specific CD⁸⁺ T cells essential for control of JC virus infection. Interestingly, natalizumab therapy substantially reduces the number of lympho-
cytes of all subsets in the cerebrospinal fluid (CSF) of treated patients with multiple sclerosis, although the effect is approximately 10-fold greater on CD4+ as compared with CD8+ T-cell subsets.18,19 This effect can last for 6 months or more after cessation of therapy. Natalizumab treatment also reduces the number of bone marrow–derived antigen-presenting cells in cerebral perivascular spaces, likely by blocking emigration of these cells from the peripheral blood into the CNS.20

Natalizumab is not the only immunomodulatory humanized monoclonal antibody that has been associated with cases of PML. Eflazumab (Raptiva) is a humanized monoclonal antibody directed against CD11a that inhibits T-cell activation, adhesion, and migration that has been licensed since October 2003 for treatment of chronic moderate to severe plaque psoriasis in adults. In 2008 and early 2009, Genentech reported that 3 patients receiving eflazumab monotherapy for treatment of plaque psoriasis had developed fatal cases of PML.21,22 Marketing authorization for the drug in Europe was suspended in February 2009 and the drug was voluntarily withdrawn from the US market in April 2009. Patients had appropriate clinical and magnetic resonance imaging (MRI) abnormalities, and diagnosis was confirmed in all cases by amplification of JC viral DNA by CSF. The first reported case (September 2008) was a 70-year-old man who had received more than 4 years of therapy. The second reported case (November 2008) was a 73-year-old woman who had received 3 years and 9 months of eflazumab therapy. The third case (February 2009) was a 47-year-old man who had received treatment for 3 years and 2 months. None of these patients had received significant other immunosuppressants. The company estimated that about 46,000 people had been treated worldwide with eflazumab as of July 2008. Of this group, about 23,500 had received less than 2 years of treatment; 1,850 had received 2 to 3 years; 700, 3 to 4 years; and 400, more than 4 years. The number of reported cases is too small to determine whether duration of therapy (>3 years in all reported cases) is related to the risk of development of PML.

Approximately 57 cases of PML have also been reported in patients receiving rituximab (Rituxan), an anti-CD20 humanized monoclonal antibody for treatment of hematologic malignancies (predominantly non-Hodgkin lymphoma)(n = 50), systemic lupus erythematosus (SLE) (n = 2),23,24 rheumatoid arthritis (n = 1), or autoimmune hematologic disorders (n = 4). The CD20 antigen is found on both pre–B cells and mature B lymphocytes and as such it predictably decreases the number of these cells and impairs humoral immune responses. However, in addition to its effects on humoral immunity, rituximab also affects cell-mediated immune responses. For example, rituximab has been reported to reduce the number of activated T cells by abolishing antigen presentation by B cells and may also increase the number of regulatory T cells.25 Given the lack of evidence that humoral immunity is critical for the control or prevention of PML (see earlier), it may be the effects of rituximab on cell-mediated immunity that enhance risk for PML.

The 2 reported fatal PML cases in rituximab-treated patients with SLE were initially reported by Genentech in December 200626 and occurred among approximately 10,000 patients estimated by the company to have received rituximab for treatment of SLE. In September 2008, the company reported an additional single case of PML in a patient with rheumatoid arthritis and Sjogren syndrome who had been receiving rituximab.27 In this case, disease was diagnosed 18 months after the last dose of rituximab, and in the posttreatment interval, the patient had received chemotherapy and radiation therapy for oropharyngeal cancer. Although it is likely that rituximab increases the risk of developing PML in patients with SLE and rheumatoid arthritis, the degree of this enhanced risk is unclear as PML has been reported in both these disorders in the absence of rituximab treatment. In 1 recent review, 35 reported cases of PML in association with rheumatic diseases were identified.11 Of this total, nearly two-thirds (n = 23) were in patients with SLE, 2 in patients with rheumatoid arthritis, 6 in patients with dermatomyositis/polymyositis, 4 in patients with Wegener granulomatosis, and 1 case in a patient with scleroderma. A review of 58 non–HIV-associated PML cases seen at the Mayo Clinic between 1957 and 2005 found that 19% had non-Hodgkin lymphoma (n = 11), 7% had SLE (n = 4), and 5% (n = 3) had rheumatoid arthritis,1 confirming that PML could occur in these conditions.

INTRODUCTION OF INFECTED ANIMALS: MONKEYPOX VIRUS

Data from the US Fish and Wildlife Service indicates that during the 5-year period of 2000 through 2004 more than 1 trillion animals of all types (including invertebrates) were imported into the United States. This number included nearly 900 million fish, 26 million amphibians, 9 million reptiles, 2 million birds, and more than 200,000 mammals.28 The “exotic pet trade” was subject to a burst of publicity in 2006 when Paris Hilton was bitten by her pet kinkajou, Baby Luv. The risk that imported exotic animals pose for the introduction of emerging pathogens was strikingly illustrated in 2003 when an outbreak of human monkeypox occurred in the midwestern United States.

Human infection with monkeypox virus was initially identified in 1970, with almost all subsequent cases confined to rainforest regions of central and west Africa. In Africa, human case fatality rates from monkeypox infection are approximately 10%, and nearly half of infected individuals develop severe complications.29 In the summer of 2003, there was an outbreak of monkeypox virus infection in 72 individuals (34 confirmed cases) in the midwestern United States, the first human infections reported from outside the African continent.30 Fifteen percent of the confirmed cases were seriously ill,31 including 1 patient with severe encephalitis.32 The most common symptoms, present in 50% or more, included rash, fever, chills and/or rigors, adenopathy, headache, myalgia, sweats, and cough.31 Rash followed the viral-like prodrome of fever, chills, headache, and myalgia after 1 to 2 days (Figure 2). The rash was maculopapular and progressed through sequential stages of papules, vesicles, and pustules. It was predominantly centrifugal and involved arms and/or hands in more than 80%, legs and/or feet in...
65%, and head and/or neck in 6%.

In the United States, as in endemic regions in Africa, monkeypox infection must be differentiated from chickenpox infection caused by varicella-zoster virus. The presence of lymphadenopathy and the propensity of the rash to involve the palms of the hands and soles of the feet are typical of orthopoxvirus infections like monkeypox but may also occur with rickettsial infection and in secondary syphilis. This distribution would be exceedingly unusual for chickenpox.

Diagnosis of monkeypox in the US cases was based on detection of orthopoxviral antigens and particles in skin biopsy specimens, isolation of virus from tissue samples, and polymerase chain reaction (PCR) amplification of viral DNA. Enzyme-linked immunosorbent assay methods for detection of IgG and IgM antibodies are now available.

The US patient with monkeypox encephalitis was a 6-year-old girl who initially presented with fever, pharyngitis, anorexia, malaise, and headache (Figure 2). On initial examination, she was noted to have adenopathy and a vesiculopapular rash. She subsequently became somnolent and unresponsive and developed presumed seizure activity. A brain MRI showed diffuse edema, meningeal enhancement, and increased signal in the thalamus and parietal cortex on fluid-attenuated inversion recovery sequences. Electroencephalogram (EEG) was diffusely slow. Cerebrospinal fluid initially had a polymorphonuclear (60%) pleocytosis (21 cells/mm³) with normal glucose and protein levels. By day 5 of hospitalization, the pleocytosis had diminished (7 cells/mm³) and converted to predominantly (80%) lymphocytes. Diagnosis was confirmed by detection of monkeypox virus IgG and IgM in serum and IgM in CSF (CSF culture and PCR results were negative) and by positive culture, immunohistochemical, and PCR results on skin lesion material. The patient gradually improved over several weeks, eventually recovering fully.

The origin of the US monkeypox outbreak was ultimately traced to a shipment of approximately 800 small mammals designed for the US pet trade originating in Ghana that occurred in April 2003. Infected animals included Gambian giant pouched rats, rope squirrels, and dormice. After arrival in the United States, the Gambian giant pouched rats were cotransported and then housed at an Illinois pet distribution center with pet prairie dogs, resulting in spread of infection to this species. Pets from the Illinois distribution center were shipped to a second distributor in Wisconsin that shipped animals to additional pet stores. Human infection was ultimately due to contact with the infected pet prairie dogs, with the first human cases appearing 5 weeks after the initial infected group of animals was imported. Seriously ill patients were more likely to have had invasive exposures to the pet prairie dogs, such as bites or scratches, although cases also occurred in individuals with frequent noninvasive contact with sick animals, such as cleaning cages or touching sick animals. Human-to-human transmission did not occur. These cases resulted in a ban on importation and limits on the sale or transport of African rodents in the United States as well as restrictions on the wild release of African rodents and pet prairie dogs.

**VECTOR SPREAD AND ENHANCED VECTOR COMPETENCE: CHIK**

There is no more dramatic example of an emerging virus infection likely due to enhanced vector competence than that caused by CHIK. The virus is a member of the alphavirus family of Togaviridae. *Aedes aegypti* mosquitoes were the principal vector, although the dramatic extension in viral host range has likely resulted from extension into *Aedes albopictus* as a vector (see later) (Figure 3).

Humans likely serve as a major mammalian reservoir. Viremia in infected humans has reached 10⁹ copies/mL, more than sufficient to infect mosquitoes and among the highest reported for arbovirus diseases. First isolated during
an epidemic in 1953 in Tanganyika (modern Tanzania), the virus causes a dengue-like illness, with cases originally concentrated in sub-Saharan Africa, India, and parts of Southeast Asia. In 2005–2006, there was an unprecedented outbreak involving 266,000 cases, more than one-third of the population of the island of La Réunion, a French territory in the Indian Ocean, likely caused by a new variant virus. Infection apparently originated in the cities of Lamu and Mombasa in Kenya in the summer of 2004 before reaching La Réunion. The epidemic subsequently spread to the Indian subcontinent, where outbreaks involving nearly 1.5 million people occurred in India, before extending to Sri Lanka and Indonesia. In some regions of India, attack rates approached 50%. In July 2007, cases suddenly appeared in 2 villages in the Ravenna Province of Italy. Two hundred fifty-four cases were ultimately identified and traced to an index case of an Indian traveler who arrived in Italy on June 21. The virus was subsequently found in native pools of A. albopictus (Asian tiger) mosquitoes, which served as the vectors for subsequent transmission.

Classic CHIK illness involves abrupt onset of fever (100%), severe arthralgia and joint swelling (80–100%), myalgia (50–60%), headache and/or back pain (50–70%), and rash (40–50%) that follows a 2- to 4-day incubation period. Diagnosis is typically confirmed by detection of serum IgG and IgM antibodies by capture enzyme-linked immunosorbent assay (available at the Centers for Disease Control and Prevention). Both IgG and IgM antibodies are present in almost all cases by day 5 after symptom onset. Reverse transcriptase (RT)–PCR amplification of viral RNA is positive at the time symptoms occur and typically remains positive until antibody responses appear, declining rapidly with the appearance of antibodies and becoming negative by day 7 in almost all cases.

Neurological disease due to CHIK is fortunately rare, but several cases of encephalitis in newborns and the elderly were identified during the onset of the epidemic in La Réunion. More recent studies have identified a broader spectrum of CNS disease including encephalomyelitis (acute disseminating encephalomyelitis), encephalomyeloradiculitis, Guillain-Barré–like syndrome, and acute flaccid paralysis. In a review of 23 cases with neurological manifestations from La Réu-

Figure 3. Vectors and distribution of chikungunya virus. A and B, Aedes albopictus (A) and Aedes aegypti (B) are the principal vectors for transmission of chikungunya virus infection. Reprinted with permission from Elsevier. C, Worldwide distribution of A. albopictus mosquitoes. Copyright 2007 Massachusetts Medical Society. All rights reserved.
union, 95% of patients had altered mental status; 30%, headaches; 26%, seizures; 9%, sensory abnormalities; and 4%, motor dysfunction, with an overall mortality of 10%. Neuroimaging studies did not show specific abnormalities. Electroencephalograms typically revealed diffuse slowing. Cerebrospinal fluid pleocytosis was only variably present.

A review of CNS infection in children identified the most common neurological presentations as encephalitis (40%), febrile seizures (33%), meningitis (13%), and acute encephalopathy (13%). Eight of 10 examined children older than 1 month had normal study results, with the 2 positive cases having increased T2 signal in cingulate, limbic areas, or white matter. Three of 4 studies performed in children younger than 1 month had abnormal results, with areas of restricted diffusion and regions of increased signal in white matter and/or cortex on T1 or T2 images. Electroencephalogram abnormalities were found in 16 of 18 examined children, typically including diffuse slowing that was anteriorly predominant in half the cases and paroxysmal polyspikes in about 40%. Mortality was 7%, and 14% had residual neurological sequelae at discharge. Cerebrospinal fluid pleocytosis was found in only 4% of examined cases, although CSF RT-PCR was positive in 61%.

The potential of CHIK to cause neurological disease is supported by data from a recently developed mouse model, which clearly shows that virus can disseminate to the CNS following peripheral inoculation, especially in neonatal mice and in adult mice lacking type I interferon signaling (interferon-α/β receptor −/−). In this model, virus invades the CNS via the choroid plexus after viremia, spreads into CSF, and infects ependymal and leptomeningeal cells but does not invade the brain parenchyma or infect neurons or glial cells. The dramatic explosion of CHIK cases was facilitated by the ability of the virus to extend its host range from Aegypti to Albopictus mosquitoes (Figure 3). Molecular studies suggest this was due to a mutation (A226V) in the viral envelope (E1) glycoprotein that was not initially present in La Réunion viral isolates but by the end of the epidemic was found in more than 90%. This mutation increases infectivity of the virus for Albopictus mosquitoes, facilitates dissemination to their salivary glands, and increases the efficiency of transmission from infected mosquitoes to vertebrate species. The ability of CHIK to efficiently infect Albopictus mosquitoes is ominous as this species is widely distributed in urban areas of Europe and the United States (Figure 3). Human travelers returning from endemic areas from India (32), Sri Lanka (3), Zimbabwe (1), and La Réunion (149). These individuals visited 17 states and the District of Columbia. Five of these individuals were found to be viremic, and 2 returned to areas of the United States where Albopictus is endemic (1 to Louisiana and 1 to South Carolina).

NEW VIRUSES

Nipah and Hendra Viruses

Emerging infectious diseases of neurological importance may also result from infection with previously unrecognized viruses. Striking examples of new neurotropic viruses are provided by Nipah and Hendra viruses. These closely related viruses are now classified in the Henipavirus genus of the family Paramyxoviridae. Hendra virus infection was first recognized in Australia in 1994 as a cause of a potentially fatal respiratory disease in horses in a stable in Hendra, a suburb of Brisbane. A pregnant mare died shortly after arrival from a paddock in nearby Cannon Hill to a stable in Hendra. Her death was followed 8 to 11 days later by a predominantly respiratory illness in 17 other horses housed in the same or adjoining stables. Five and 6 days after the mare’s death, a 40-year-old stable hand and a 49-year-old trainer who had close contact with the dying mare became ill. The stable hand recovered after a flulike illness, but the trainer died after a 6-day severe systemic illness that included severe interstitial pneumonia leading to respiratory failure, complicated by renal failure, arterial thrombosis, and cardiac arrest. The causative agent was identified as a novel member of the Morbillivirus genus of the family Paramyxoviridae. Hendra virus infection has already been reported in the United States of Europe and the United States (Figure 3). Human infection was first recognized in Australia in 1994 as a cause of a potentially fatal respiratory disease in horses in a stable in Hendra, a suburb of Brisbane. A pregnant mare died shortly after arrival from a paddock in nearby Cannon Hill to a stable in Hendra. Her death was followed 8 to 11 days later by a predominantly respiratory illness in 17 other horses housed in the same or adjoining stables. Five and 6 days after the mare’s death, a 40-year-old stable hand and a 49-year-old trainer who had close contact with the dying mare became ill. The stable hand recovered after a flulike illness, but the trainer died after a 6-day severe systemic illness that included severe interstitial pneumonia leading to respiratory failure, complicated by renal failure, arterial thrombosis, and cardiac arrest. The causative agent was identified as a novel member of the Morbillivirus genus of the family Paramyxoviridae. Hendra virus infection has already been reported in the United States.
nippoviruses could produce CNS disease, this was unequivocally established by the emergence of Nipah virus in Singapore and Malaysia in 1998. Between September 1998 and December 1999, a series of outbreaks of febrile encephalitis occurred among pig-farm workers and residents of several pig-farming villages in the states of Perak and Negeri Sembilan in Malaysia. In the initial episodes, virtually all those affected (93%) were pig farmers or worked in occupations that brought them in close contact with pigs. In 1999, 9 cases of encephalitis and 2 of pneumonitis occurred in Singapore in abattoir workers involved in processing pigs imported from Malaysia. A total of nearly 300 encephalitis cases eventually occurred in Singapore and Malaysia, with an overall mortality approaching 40%.

In Malaysia and Singapore, the majority of affected cases were men, reflecting the occupational exposure. The incubation period was less than 2 weeks in 90% of cases and the majority of infected individuals (55%-85%) developed symptomatic illness. Central nervous system disease was typically preceded by a 3- to 4-day prodrome of fever, nausea, myalgia, and dizziness. The initial presenting features, based on a series of 94 total cases from the initial and subsequent outbreaks in Malaysia, included fever (87%), headache (65%), dizziness (36%), and vomiting (27%). Neurological signs included reduced tendon reflexes (56%), segmental myoclonus (32%), mastic rigidity (28%), and seizures (23%) and cerebellar abnormalities (9%). A compilation of 92 cases from outbreaks between 2001 and 2004 in Bangladesh found the most common clinical characteristics to be fever (100%), altered mental status (90%), headache (73%), respiratory difficulty (69%), severe weakness (67%), and seizures (23%). Overall mortality was 73%. In the Malaysian series, common laboratory abnormalities included a CSF pleocytosis (75%-85%) with mean cell counts of approximately 40/mm³, elevated protein level (mean, 69 mg/dL), and a normal glucose level. Neurological signs included reduced tendon reflexes (56%), segmental myoclonus (32%), mastic rigidity (28%), and seizures (23%) and cerebellar abnormalities (9%). A compilation of 92 cases from outbreaks between 2001 and 2004 in Bangladesh found the most common clinical characteristics to be fever (100%), altered mental status (90%), headache (73%), respiratory difficulty (69%), severe weakness (67%), and seizures (23%). Overall mortality was 73%. In the Malaysian series, common laboratory abnormalities included a CSF pleocytosis (75%-85%) with mean cell counts of approximately 40/mm³, elevated protein level (mean, 69 mg/dL), and a normal glucose level.

The frequency of CSF pleocytosis appears to be variable, as another series found that only 1 of 6 laboratory-confirmed cases had more than 9 cells/mm³. Computed tomographic scan was usually normal but MRI was abnormal in almost all patients examined. The most common finding was multiple small (2- to 7-mm) areas of increased T2 and fluid-attenuated inversion recovery signal in the subcortical and deep white matter, usually without mass effect or edema (Figure 4).

Less commonly, abnormalities were also found in the cortex, thalamus, and brainstem. Electroencephalogram, when performed, was abnormal, showing either diffuse slowing or periodic slow wave complexes. Serum IgM was detectable in almost all patients early after illness onset, and IgG was found in virtually all cases by 2 to 3 weeks. Specific therapy is available, although ribavirin reduced mortality from 54% to 32% in an open-label trial. One of the most unusual features of Nipah infection is the propensity for patients to develop relapsing and/or late-onset encephalitis. Late-onset encephalitis, in patients who do not initially have neurological symptoms, occurs in about 3% of cases. Eight percent of survivors of acute encephalitis had recurrent neurological disease (relapsed encephalitis). The interval between initial infection and relapse averaged about 8 months. In patients with a second relapse, this occurred an average of 8 months after the first relapse. In all cases, relapse presented acutely. Patients with relapses were less likely to have fever (46%) and headache (42%) and more likely to have seizures (50%) and focal neurological signs (42%) than those with acute encephalitis. As in acute encephalitis, CSF was usually abnormal (79%) with a mean cell count of 59/mm³. In distinction to the acute disease, in which lesions occurred predominantly in the white matter, many patients had larger confluent or patchy corticomedial and subcortical hyperintensities on T2 and fluid-attenuated inversion recovery sequences.

The largest autopsy series reported to date (32 cases) revealed several unusual features of Nipah encephalitis. Patients often had a systemic vasculitis associated with thrombosis and parenchymal necrosis, which was particularly common in the CNS. Viral antigen and viral inclusions were often seen in cerebral vascular endothelial cells. An unusual, and perhaps pathognomonic finding, was the presence of syncytial multinucleated endothelial cells, which was seen in 25% of cases and had only previously been described in Henipavirus encephalitis (see earlier). Vascular thrombosis and vasculitis were often seen in proximity to multifocal necrotic plaques, which likely corresponded to the acute lesions seen on MRI (see earlier). Inflammatory infiltrates occurred near the necrotic plaques. Neuronophagia, microglial nodule formation, and perivascular cuffing were also common, and viral inclusions and viral antigen could be detected in the cytoplasm and nuclei of neurons. In contrast to patients who had died of acute encephalitis, brains from patients who had relapsed encephalitis did not show vas-
culitis or necrotic plaques. In these cases, neuronal injury was more extensive and viral inclusions were more prominent. These findings suggest that Nipah originally spreads to the CNS through the bloodstream and that the initial neurological manifestations are the result of a multifocal vasculitis with resulting multicentric thrombosis as well as to direct infections of neurons. In contrast to the acute illness, relapsing encephalitis appears to be due to reactivation of neuronal infection, rather than vasculitis and ischemic thrombosis.

In 2001-2004, a series of new outbreaks of Nipah virus encephalitis occurred in India and Bangladesh. Symptoms were similar to those described initially, but mortality in some areas approached 75%. Unlike the prior outbreaks, none of the affected individuals had exposure to pigs or pig products. It was subsequently discovered that the natural reservoir for Nipah were likely flying foxes and fruit bats (Pteropid species) and that virus was likely shed from bats in their urine. Animals such as pigs and horses could contract infection from either direct exposure to bat urine or through exposure to fruit contaminated by bat urine. Once infected, pigs were able to transmit infection laterally to other pigs. Human-to-human transmission was not a feature of the initial outbreaks in Malaysia and Singapore, but the absence of exposure to animal reservoirs of infection in subsequent outbreaks suggests that this is an important mode of disease transmission.

Humans, like other infected mammals, shed virus in saliva, nasopharyngeal secretions, and urine.

In 2001, a Nipah outbreak occurred in a hospital in Siliguri, India (near Bangladesh), involving 11 hospitalized patients, 25 members of the medical staff, and 8 visitors. Epidemiological studies of the outbreak were clearly consistent with spread of infection from hospitalized patients to medical staff and visitors. Clinical features included fever (100%), altered mental status (97%), headache (57%), respiratory dysfunction (51%), and apparent seizures (43%). Mortality was 63%.

Bat Lyssaviruses

Another striking example of the emergence of new viruses as human pathogens involves members of the Lyssavirus genus of the family Rhabdoviridae, a group that includes classic rabies virus. A series of viruses, closely related antigenically to rabies virus but genetically distinct, have now been isolated from bats in Europe and Australia (European and Australian BLV, previously designated Pteropid lyssaviruses). In 1996, a fatal case of human BLV infection occurred in a 39-year-old woman involved in care of bats who had a history of numerous bat scratches on her arm. Four weeks later, she developed progressive arm weakness followed by brainstem symptoms (diplopia, dysarthria, dysphagia), ataxia and cerebellar signs, bilialeral weakness, and progressive flaccid quadriaparesis progressing to death. During her illness, she had a CSF lymphocytic pleocytosis (100 cells/mm³). Her EEG showed periodic slow activity that was anteriorly predominant, and MRI showed foci of increased T2 signal in the pons. Serologic results showed a rise in rabies virus–neutralizing antibody titer, and RT-PCR of both CSF and brain tissue amplified nucleic acid sequences from Australian BLV. At autopsy, she was found to have a meningoencephalitis with neuron loss concentrated in the cerebellum (Purkinje cells) and hippocampus and associated neuronophagia and microglial nodules. Neurons contained oval eosinophilic cytoplasmic inclusions that were similar to but smaller and less well defined than typical Negri bodies (Figure 5).

A second human case of fatal BLV infection was reported from Australia in 1998 and involved a 37-year-old woman who had been bitten on her finger by a flying fox. Twenty-seven months later, she developed fever, shoulder and hand pain, and paresthesias. Her illness rapidly progressed and she developed fever, dysarthria, dysphagia, increased muscle tone and muscle spasms, and hydrophobia-like spasmodic swallowing. She became ventilator dependent and died. Reverse transcriptase–PCR of her saliva, but not of serum or CSF, amplified sequences from Australian BLV. At autopsy, she was found to have severe encephalitis maximally involving the brainstem and hippocampi. As in the previous case, there was neuronal loss, neuronophagia, microglial activation, perivascular lymphocytic cuffing, and inclusions. Polymerase chain reaction–amplified Australian BLV sequences from brain and immunofluorescence with anti–Australian BLV serum samples were diffusely positive in brain tissue. Virus was also cultured from brain tissue in neuroblastoma cells and confirmed to be Australian BLV.

Two cases of well-documented human BLV infection have been reported from Europe, and 2 possible additional cases have occurred in Ukraine and Russia. The most recent case (2002) involved a 55-year-old man with a history of bat bites who developed a similar syndrome of radicular pain and paresthesias, altered mental status, dysarthria, dysphagia, and ataxia that rapidly progressed to agitation, respiratory failure, and ultimately
death. He had a CSF lymphocytic pleocytosis (20 cells/mm³) and elevated protein level. Electroencephalogram showed an “encephalitic pattern” and electromyogram/nerve conduction velocity studies were consistent with generalized acute denervation. A noncontrast computed tomographic scan was normal and MRI was not performed. Diagnosis was confirmed by detection of BLV nucleic acid by RT-PCR from saliva and confirmed post mortem by virus isolation from brain and positive RT-PCR on brain tissue.

Previously unrecognized new rabies virus variants originating from bats and causing fatal human disease have also recently been reported in the United States. However, the bat viruses linked to rabieslike human disease isolated to date in the United States are variants of classic rabies virus rather than belonging to the distinct Lyssavirus lineages seen in the European and Australian cases.

THE FUTURE

When asked in 1927 to explain the uncertainty principle in physics, Sir Arthur Eddington is said to have replied, “Something unknown is doing we don’t know what.” This would also appear to be an apt summary of the current state of knowledge concerning emerging infectious diseases. We can state with certainty that the list of microbial pathogens causing human disease will continue to change with both the disappearance of current pathogens, as a result of natural processes or more hopefully owing to successful human interventions, and the continued emergence of novel agents. Changes in world ecology, driven in significant part by human activities, will continue to impact the distribution of vectors involved in the transmission of diseases and their hosts, as well as increase the opportunities for human exposure to disease-transmitting vectors. As human habitation expands, and agricultural and other human activities change the environment, new situations for human exposure to novel pathogens will only increase. Rapidly progressing technological advances will increase our ability to alter elements of the host’s acquired and innate immune systems as we strive to improve treatment of autoimmune diseases and reduce the risk of transplant rejections. The price of these advances will also be the unpredictable emergence of opportunistic infections. The application of new molecular biological techniques, exemplified by high-throughput large-scale genome sequencing, will revolutionize our ability to rapidly diagnose certain types of infectious diseases, identify novel and unexpected pathogens involved in the pathogenesis of diseases, and identify host genetic factors involved in disease susceptibility. The challenge will be to be sure that parallel advances in our understanding of host immune responses and of pathogen replication and pathogenesis enable us to develop novel strategies for disease prevention and therapy.

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REFERENCES


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