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NEUROLOGICAL INFECTIONS IN THE RETURNING INTERNATIONAL TRAVELER

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Abstract

Clinicians may encounter international travelers returning with exotic infections, emerging infectious diseases, or resurgent old-world infections. Many of these infectious diseases can affect the nervous system directly or indirectly. The contemporary neurologist should therefore be cognizant of the clinical manifestations, potential complications, and appropriate management of common travel-related infections. This chapter focuses on five important infections that affect the central nervous system and that may be encountered in returning travelers: Japanese encephalitis, malaria, rabies, dengue, and neurocysticercosis. The clinical manifestations, suggested evaluation, and treatment are discussed for each infection.

INTRODUCTION

Over 50 million Europeans and North Americans traveled to tropical countries for professional, social, recreational, and humanitarian purposes during 2000 (Dawood, 2002). Foreign travel exposes travelers to new environments and activities. With the increasing popularity of group tours, wildlife expeditions, and adventure sports, more travelers are potentially exposed to environments containing endemic tropical infections (Stephens et al, 1998). In addition, newly emergent infections and appearance of drug-resistant organisms continually change the spectrum of potential neurological infections in travelers. Over 30 new infections such as Ebola, Nipah virus, and Hantavirus have emerged over the past few decades (Centers for Disease Control and Prevention, 1999). Changes in ecosystems have also contributed to the spread of some tropical infections to different continents, most notably West Nile virus, dengue, and Japanese encephalitis (Centers for Disease Control and Prevention, 1999; Stephens et al, 1998).

The World Tourism Organization (2004) estimated that 214.5 million people traveled to Central or South America, Africa, or Asia during 2003. In one study of 10,524 travelers to developing countries, 15% reported developing illness associated with the trip, 8% consulted a doctor, and 3% were unable to work for an average of 15 days (Steffen et al, 1987). In an Australian study, 1% of travelers presenting with a febrile illness were diagnosed with meningitis or encephalitis (O'Brien et al, 2001). The number of travelers returning with central nervous system (CNS) infection is likely to be underestimated due to inadequate reporting and poor case ascertainment. With increasing travel, immunosuppression (either acquired or induced), organ transplant, or malignancy, the spectrum and incidence of “tropical” infections will likely expand. Although infections of the nervous system are uncommon, increasing international travel exposes more people to infections that have potential neurological manifestations. Travel history, neurological examination, and

neuroimaging should guide diagnostic and therapeutic decisions. Neurological symptoms, neuroimaging findings, and diagnostic testing for the five infections discussed in this chapter are presented in Table 6-1. Available treatments and vaccinations, as well as electronic and text resources are listed in Tables 6-2 and 6-3.

Most travel-related infections can be minimized or prevented by suitable precautions taken before or during travel. Travelers should consult a travel medicine clinic to determine if vaccinations or prophylactic medications are indicated. This consultation should preferably take place 4 to 6 weeks before the journey. Medical advice should be based upon an individualized risk assessment, taking into account the likelihood of acquiring an infection and perceived concern of the traveler. The key elements of this risk assessment include destination, duration and purpose of travel, conditions of accommodation, and health status of the traveler. Special precautions may be necessary for certain high-risk travelers, including infants, pregnant women, elderly persons, disabled persons, and people with immunosuppression or preexisting health problems. Travelers who have lived in foreign countries for more than 6 months should also receive an evaluation upon return.

DENGUE

Dengue is present in virtually every country in the southern hemisphere and is the arboviral infection international travelers are most likely to encounter (Bhatoe et al, 2000). Dengue affects 100 million people worldwide each year, and 2.5 billion people— two fifths of the world's population— are at risk of contracting infection (Gubler, 1998; World Health Organization, 2005b). Dengue virus is a flavivirus transmitted by the bite of *Aedes aegypti* or *Aedes albopictus* mosquito. Four dengue virus serotypes (1 to 4) have been identified, all of which have been associated with neurological disease (Gubler et al, 1983). In one study in Thailand, 18% of children hospitalized with an encephalitislike illness had dengue infection (Pancharoen et al, 2001).

Clinical Manifestations

Symptoms usually develop 4 to 7 days after the mosquito bite (World Health Organization, 1997). Most cases present with dengue fever, also known as breakbone fever, a self-limited influenzalike illness with high fever, headache, retrobulbar pain, and myalgias. A more severe illness, dengue hemorrhagic fever, occurs only in people previously infected with dengue. Manifestations include hemorrhagic diathesis, thrombocytopenia, and increased vascular permeability leading to a serious complication called dengue shock syndrome (World Health Organization, 2005b).

Neurological symptoms are common during dengue but are most often attributed to encephalopathy rather than direct CNS infection. Dengue virus has been detected in brain and CSF using immunohistochemistry, polymerase chain reaction (PCR), and immunoglobulin assays, consistent with direct CNS infection (Lum et al, 1996; Ramos et al, 1998; Solomon et al, 2000). Three distinct neurological syndromes have been reported during dengue infection:

- (1) *Acute, nonspecific neurological symptoms.* During acute dengue infection, headache and retrobulbar pain occur in most people (World Health Organization, 1997). In addition, sleeplessness, restlessness, and mood change are common.
- (2) *Acute, encephalitic or focal neurological symptoms.* Neurological dysfunction develops in up to 5% of people with dengue and may manifest as spastic paraparesis, Guillain-Barré syndrome, Bell's palsy, mononeuropathy or polyneuropathy, or seizures (Pancharoen and Thisyakorn, 2001, Solomon et al, 2000). Seizures occur in up to 16% of children with primary dengue infection (Mehendale et al, 1989). Encephalitis occurs infrequently, except in children living in Asia and is more likely to occur during the acute illness (Lum et al, 1996). Some patients may have disease limited to the spinal cord (Yamamoto et al, 2002).
- (3) *Postinfectious neurological complications.* Postinfectious complications are more likely to occur in adults and may include palsy (facial, palatine, ulnar, long thoracic, and peroneal) or transverse myelitis (Kaplan and Lindgren, 1945; Solomon et al, 2000).

Diagnosis

Confirmatory diagnosis is made by detection of dengue-specific IgM in serum, a fourfold rise in dengue-specific immunoglobulin G (IgG) titer (CSF or serum) or identification of virus in the CSF by PCR (De Paula et al, 2002; Kankirawatana et al, 2000). Antibody can cross-react with other flavi-viruses (eg, Japanese encephalitis virus). Analysis of CSF typically reveals elevated protein and mild lymphocytic pleocytosis (Kankirawatana et al, 2000; Lum et al, 1996; Mehendale et al, 1989; Solomon et al, 2000). Computed tomography (CT) or magnetic resonance imaging (MRI) may show cerebral edema or evidence of encephalitis on T2-weighted and FLAIR sequences (Cam et al, 2001; Kankirawatana et al, 2000; Lum et al, 1996) (**Case 6-1**).

Treatment

Treatment is supportive; severe cases require intensive care. The case fatality rate varies by country from less than 1% to over 20% (World Health Organization, 2005b). In one review of 168 people with encephalopathy due to dengue who had outcomes measured, the mortality rate was 58%; of the remaining 42%, all but four had complete recovery (Angibaud et al, 2001). No dengue vaccines are available to date. However, attenuated candidate vaccine viruses have been developed in Thailand, and second-generation recombinant vaccine viruses are under development (Chaturvedi et al, 2005; Sabchareon et al, 2002). Public health measures aimed at controlling dengue vectors through reduction or elimination of breeding areas for *A. aegypti* and *A. albopictus* have been successful in reducing the incidence of dengue epidemics in some countries (Kay et al, 2002).

JAPANESE ENCEPHALITIS

Although considered by many in the West to be a rare and exotic infection, Japanese encephalitis is probably the most important viral encephalitis worldwide. The infection was originally identified in Japan but over the past 50 years has spread throughout Southeast Asia, the Indian subcontinent, China, and the Pacific Rim. Epidemics occur in late summer in temperate regions, but in many tropical areas of Asia infection occurs throughout the year. Approximately 30,000 to 50,000 cases of encephalitis and 15,000 deaths are reported each year, mostly in children, but fewer than 1 case per year occurs in US civilians or military personnel traveling to or living in Asia. Japanese encephalitis is caused by Japanese encephalitis virus, a flavivirus related to dengue and West Nile virus, which is maintained in a life cycle involving mosquitoes and aquatic birds. The virus is transmitted to humans by *Culex* mosquitoes, primarily *Cx tritaeniorhynchus*, which breed in rice fields. In residential environments, pigs are the main amplifying host of Japanese encephalitis virus (Bengis et al, 2004).

Clinical Manifestations

The incubation period of Japanese encephalitis is 5 to 14 days (Bengis et al, 2004). Most infections are asymptomatic with only one of every 30 to 300 infected people developing symptoms (Dawood, 2002). Mild infections produce a flulike illness that resolves within 5 to 7 days (**Case 6-2**). More serious infections are associated with meningoencephalitis or other CNS manifestations (Richter and Shimojyo, 1961). Patients initially present with fever, headache, and vomiting and progress rapidly. CNS complications during the acute illness include delirium, seizures, axial rigidity, movement disorders, cranial nerve palsies, ataxia, paraplegia, and segmental sensory disturbances (Lowry et al, 1998). Movement disorders such as parkinsonism and dystonias may persist beyond the acute phase of illness (Murgod et al, 2001). A new recently described variant predominantly affects the spinal cord, causing acute flaccid paralysis similar to the acute flaccid paralysis that may occur with West Nile virus infection (Solomon et al, 1998).

Diagnosis

Japanese encephalitis is confirmed by detection of virus-specific IgM antibodies in the CSF or serum by enzyme-linked immunoabsorbent assay (ELISA) (Martin et al, 2002). Lymphocytic pleocytosis is common in CSF of patients with Japanese encephalitis (Misra et al, 2003). Neuroimaging abnormalities include T2-weighted signal changes in the basal ganglia, substantia nigra, pons, cerebral cortex, or cerebellum (Kalita et al, 2003; Misra et al, 2003).

Treatment

Most infections are treated with conservative management. The mortality rate in most outbreaks is less than 10% but in children can exceed 30%. Neurological sequelae occur in up to 30% of patients who survive severe infection (Richter and Shimojyo, 1961). In one study of survivors of severe Japanese encephalitis, neurological deficits were common and included quadriplegia (60%), hemiplegia (12%), muscle wasting (25%), and seizures (50%) (Kalita et al, 2003). Poor outcome is associated with detection of virus in the CSF, low level

of virus-specific antibody in the CSF or serum, and decreased level of consciousness (Misra et al, 2003). A formalin-inactivated vaccine prepared in mice is used widely in Japan, China, India, Korea, Taiwan, and Thailand (Monath, 2002; Solomon, 2003). This vaccine is also available in the United States for travelers to endemic countries. The Centers for Disease Control and Prevention (CDC) (2005a) recommends completion of three vaccinations at least 10 days prior to departure due to the potential risk of a delayed hypersensitivity reaction (angioedema) associated with vaccination. Although interferon alpha showed antiviral activity against Japanese encephalitis virus in animal models, a randomized trial in humans demonstrated no beneficial effects (Solomon et al, 2003).

CEREBRAL MALARIA

Malaria is a febrile illness common in travelers to Africa, Central and South America, and Southeast Asia (O'Brien et al, 2001). Of the 125 million people from nonendemic countries who travel through malaria-endemic countries each year, 10,000 to 30,000 will contract malaria (Centers for Disease Control and Prevention, 2003; World Health Organization, 2005a). Over 1000 cases of malaria occur each year among tourists from the United States (Stoppacher and Adams, 2003). Malaria is caused by *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae* and is transmitted by mosquito bite. Approximately 90% of *falciparum* malaria is acquired in sub-Saharan Africa, and 70% of *vivax* malaria is acquired in Latin America and Asia (Centers for Disease Control and Prevention, 2003). *Falciparum* malaria is the most common cause of cerebral malaria.

Clinical Manifestations

Cerebral malaria is characterized by an unarousable state accompanied by parasitemia (most often *P. falciparum*), and diagnosis requires exclusion of other etiologies, such as hypoglycemia, postictal sedation, or other CNS infection (World Health Organization, 2005b). Cerebral malaria most often occurs in pregnant women, children, nonimmune populations, and people taking inadequate chemoprophylaxis (Newton et al, 2000). Initial symptoms are nonspecific and include intermittent fever with chills, headache, nausea, vomiting, abdominal pain, and myalgias followed by stupor and coma (**Case 6-3**). Cranial nerve dysfunction such as horizontal or vertical nystagmus, ocular bobbing, or sixth nerve palsy is occasionally present (Oluimese et al, 1999). Seizures occur in 20% to 50% of patients with cerebral malaria and are typically focal and recurrent (Meremikwu and Marson, 2002). Coma may develop precipitously or subacutely following a generalized seizure and typically lasts 1 to 3 days (Mackintosh et al, 2004). The mortality rate of cerebral malaria is 20% to 50% (Newton et al, 2000). The incidence of epilepsy in survivors of cerebral malaria is unknown. In contrast to cerebral malaria, patients who recover from severe malaria without CNS involvement can have a self-limited acute confusional state when parasites are not detectable in the blood; this syndrome is called the postmalarial neurological syndrome and is more common in people treated with mefloquine (Nguyen et al, 1996).

Diagnosis

Examination of thick and thin blood smears with Giemsa staining can detect parasitemia and identify malarial species. Serological tests (ParaSight-F and immunochromatographic malaria *P. falciparum* test) are available, but false-positive tests are common (Kodisinghe et al, 1997). CT may demonstrate cerebral edema during the advanced stages of cerebral malaria, and transtentorial herniation is a common CT or MRI finding in fatal cases (Looareesuwan et al, 1983). MRI may reveal brain swelling without edema or multifocal (often symmetrical) white matter hyperintensities (Cordoliani et al, 1998; Looareesuwan et al, 1995).

Treatment

Choice of treatment should be guided by *Plasmodium* species prevalent in the region where infection was acquired, severity of malaria, and *Plasmodium* species present in blood smear. Treatment should be initiated immediately after diagnosis is confirmed or when malaria is highly suspect. Chloroquine-resistant *P. falciparum* is present in Southeast Asia, the Amazon region of South America, and certain areas of sub-Saharan Africa. In these areas, quinine with doxycycline, mefloquine, or newer antimalarial drugs (eg, artemisinin derivatives) should be used (Tran et al, 1996). For the traveler with suspected cerebral malaria due to chloroquine-resistant or *Plasmodium* with unknown resistance, initial treatment should include intravenous quinine, but in the United States quinine is not available, so quinidine should be substituted. Due to the complicated nature of treating malaria, treatment guidelines should be consulted (Centers for Disease Control and Prevention, 2005b). Patients with cerebral malaria who are treated with steroids have a poorer outcome than those who do not receive them; thus steroids should not be administered to patients with cerebral malaria (Hoffman et al, 1988; Warrell et al, 1982). In addition, although anticonvulsants are indicated for patients with cerebral malaria who develop seizures, routine prophylactic use of anticonvulsants may be associated with worse outcome (Meremikwu and Marson, 2002; Molyneux et al, 1989).

RABIES

Rabies is a preventable, fatal viral encephalomyelitis caused by rabies virus, a member of the Lyssavirus genera of the Rhabdoviridae family; several other Lyssavirus members also cause an encephalitis that is indistinguishable from rabies (Warrell and Warrell, 1988). Rabies is present in parts of Africa; Asia; and North, Central, and South America (Knobel et al, 2005; Wilde et al, 1999). The infection is most commonly transmitted by the bite of a rabid animal (Bengis et al, 2004). In the United States, wild animals such as raccoons, skunks, bats, and foxes are the most common animal reservoirs, and domestic animals (ie, dogs and cats) account for less than 10% of infections (Noah et al, 1998). Human rabies caused by bite of a rabid dog is more common in areas of the world where canine rabies is not controlled through immunization or stray animal removal. Molecular techniques can be used to identify the source of the virus. The virus has been transmitted in saliva via the bite of a rabid animal, in aerosolized fluid inhaled by cave explorers, or in corneal transplant. Recently, several cases of rabies infection occurred in organ transplant recipients (Burton et al, 2005; Lapierre and Tiberghien, 2005; Roos, 2005). After an incubation period of several

weeks to months, the virus passes via the peripheral nervous system and replicates in the CNS (Hankins and Rosekrans, 2004).

Clinical Manifestations

Classic rabies presents in either the encephalitic (furious) form with fluctuating consciousness, phobic spasms, and autonomic dysfunction, or the paralytic (dumb) form, which presents with weakness or sensory symptoms in the bitten limb progressing to generalized paralysis; symptoms similar to Guillain-Barré syndrome have also been described (Hemachuda, 2005; Hankins and Rosekrans, 2004). Nearly all patients with encephalitic rabies develop pharyngeal spasms when offered water (hydrophobia) or exposed to moving air (aerophobia) (**Case 6-4**). The patients who developed rabies following transplantation initially presented with nonspecific systemic symptoms prior to developing fulminant neurological disease (Burton et al, 2005). Following the onset of neurological symptoms, generalized flaccid paralysis, respiratory and vascular collapse, and coma develop with most deaths occurring within 2 weeks after onset of coma; as the illness progresses to these final stages, the encephalitic and paralytic forms present similar manifestations.

Diagnosis

Several tests are available to diagnose rabies antemortem in humans: histo-pathology, viral nucleic acid or antigen detection, virus isolation, and serology (Meslin et al, 1996). Tests can be performed on saliva, pharyngeal swab, serum, CSF, or biopsy of brain or skin containing hair follicles at the nape of the neck. Rabies virus can be detected in saliva or CSF by culture or reverse transcription-PCR (Wacharapluesadee and Hemachudha, 2001). Rabies virus antigen detection within nerve cells in the brain or skin biopsy using fluorescent antibody technique is highly specific and sensitive (Bingham and Mlambo, 1995). Serum and spinal fluid can be tested for antibodies to rabies virus in people who have not been previously vaccinated (Crepin et al, 1998). CSF examination may reveal mild lymphocytic pleocytosis with normal glucose and increased protein concentration (Hemachuda et al, 2005; Warrell and Warrell, 1988). Postmortem diagnosis is made by histopathological examination of brain tissue and meninges, which demonstrates mononuclear infiltration, lymphocytic or polymorphonuclear perivascular cuffing, neuronal degeneration, and Negri bodies (Hemachudha et al, 2005). Negri bodies are round or oblong intracytoplasmic inclusions consisting of viral nucleocapsid proteins. Neuroimaging abnormalities that have been described include increased T2-weighted or FLAIR signal abnormalities in the brain stem, cortex, subcortex, hippocampus, hypothalamus, and basal ganglia, as well as enhancement of these areas after administration of gadolinium (Burton et al, 2005).

Treatment

After the bite or scratch of an animal suspected to have rabies, local public health authorities should be contacted for assistance with diagnosis and postexposure prophylaxis. When possible, the animal should be captured for testing. Pre-exposure vaccination is recommended for travelers who anticipate prolonged stays in rural areas with high levels of

endemic rabies, especially cave explorers (Advisory Committee on Immunization Practices, 1999). Rabies should be included in the differential diagnosis of undiagnosed encephalopathy in any patient returning from a country where rabies is endemic (Fooks et al, 2003). Treatment of a person exposed to rabies varies by vaccination status: if previously vaccinated, the person should receive rabies vaccine intramuscularly in the deltoid area on days 0 and 3; if not previously vaccinated, vaccine as well as rabies immune globulin (20 IU/kg infiltrated into or around the wound and intramuscularly) should be administered. After symptoms of rabies have developed, the infection is almost uniformly fatal, although some survivors have been reported (Willoughby et al, 2005).

NEUROCYSTICERCOSIS

Neurocysticercosis (NCC) is perhaps the most common cause of epilepsy in the developing world (Senanayake and Roman, 1993). Humans are the only definitive host of *Taenia solium*, the tapeworm responsible for NCC. Two types of infection can occur in humans: (1) taeniasis, an intestinal tapeworm infection caused by eating undercooked pork containing cysticerci (larva); and (2) cysticercosis, an infection caused by ingestion of *T. solium* eggs excreted in the feces of a human with taeniasis. After ingestion of the egg, the larval form (oncosphere) hatches and migrates to sub-cutaneous tissue, muscle, or nervous system. Pigs are an intermediate host and can acquire cysticercosis by eating *T. solium* eggs in human waste but do not develop adult tapeworm infection. *T. solium* infection is endemic throughout the world. Seroprevalence rates range between 5% and 11% in Mexico, Peru, and Ecuador (Pittella, 1997). In Brazil, the seroprevalence of antibodies to *T. solium* is 0.7% to 5.2%, with the highest rates in rural areas. In other parts of the world, seroprevalence rates vary from 13% in Bali to 4% in Korea and 18% in Madagascar. In the United States, government inspection typically identifies 10 cases of cysticercosis in the 80 million hogs slaughtered each year (Schantz and McAuley, 1991).

Clinical Manifestations

Symptoms and signs of NCC typically occur many years after initial infection, and are associated with host immune response induced by release of *T. solium* antigens from the dying parasite. A host-mediated inflammatory immune response causes the death of the parasite (Pittella, 1997). Neurological symptoms of NCC may be acute, chronic, or relapsing and are determined by the location of the cyst(s) within the neuraxis. NCC may mimic stroke, tumor, carotid artery occlusion, or intracerebral hemorrhage (Cantu and Barinagarrementeria, 1996). Fifteen percent of people with NCC have cysts in the ventricular system, the majority located in the fourth ventricle. Cysts within the ventricles are often difficult to visualize with neuroimaging but can be identified if imaging with intraventricular contrast is performed at the time of shunting (Apuzzo et al, 1984). An uncommon but serious form of infection is racemose cysticercosis: a cluster of interconnected grapelike cysts without an identifiable scolex. Racemose cysticercosis most often occurs around the brain stem or within the ventricles and frequently causes hydrocephalus. Another serious form of NCC that occurs most commonly in young women is encephalitis; this form is often associated with severe cerebral edema. Extraneural cysticercosis may occur in skeletal musculature, conjunctiva, or retina but is rarely present

in persons with NCC. Little information is available regarding coinfection of NCC and human immunodeficiency virus (HIV). Of the few case series published, there is a suggestion that the racemose form of NCC may be more common in patients coinfecting with HIV, but no large series have further examined this hypothesis (Delobel et al, 2004; Soto Hernandez et al, 1996; Thornton et al, 1992). Reports of patients with NCC in the setting of other immunosuppressive states suggest disease may be more severe in the immunocompromised, but large series have not been published (Sanz, 1987). As the host immune response is responsible for clinical symptoms associated with neurocysticercosis, it is not clear why people with immunosuppression would develop more severe manifestations of infection.

Diagnosis

Neurocysticercosis is diagnosed by neuroimaging and serological testing (**Case 6–5**). Del Brutto and colleagues (1996) proposed diagnostic criteria for NCC that combine histological, radio-graphic, immunological, and clinical evidence. Definitive diagnosis of NCC can be made if the following are present: (1) histopathological evidence of NCC; (2) a scolex within a cystic lesion visualized by CT or MRI; or (3) lesion(s) suggestive of NCC by neuroimaging with serological evidence of *T. solium* infection by serum enzyme-linked immunoelectrotransfer blot or CSF ELISA. Serum ELISA may be more sensitive than CSF ELISA. The sensitivity of serum ELISA is only 50% in people with a single intraparenchymal CNS lesion. The CSF is most often normal in persons with NCC, but a mild lymphocytic pleocytosis can occur.

CT and MRI of people with NCC typically reveal single or multiple cysts with variable calcification, cyst wall enhancement, or surrounding edema. Compared with CT imaging, MRI is superior for detection of the racemose form of NCC, the scolex of the parasite, and additional cysts. Escobar (1983) described four imaging stages of NCC. Infection typically begins as one or more areas of noncontrast-enhancing areas of edema. This progresses to homogeneous contrast-enhancing lesions, then nonenhancing cystic lesions, followed by ring-enhancing cystic lesions with or without edema, and finally to complete resolution or calcification.

Treatment

Controversy exists regarding treatment of NCC. Experts agree that most symptomatic NCC occurs during the inflammatory response induced by death of the cyst. If neuroimaging reveals only calcified or ring-enhancing cysts (inactive infection), treatment is probably not necessary. People with homogeneously enhancing or hypodense lesions (active infection) should receive treatment with albendazole or praziquantel; both anthelmintics are cysticidal (Del Brutto et al, 1996). Some clinical trials report more favorable outcomes with albendazole, especially if subarachnoid cysts are present (Takayanagui and Jardim, 1992). For people with multiple cysts, steroids should be administered 1 to 3 days prior to administration of anthelmintics and continued over the course of treatment to reduce edema associated with treatment. Steroids lower the plasma level of praziquantel and increase the plasma level of albendazole (Jung et al, 1990). Treatment has been associated with long-term improvement of seizures and with decrease in number and size of intraparenchymal

lesions (Vazquez and Sotelo, 1992). If treatment is not indicated, seizures should be treated with anticonvulsants. Close contacts of people with NCC should undergo serological testing for *T. solium* infection and be imaged if they are sero-positive and have neurological symptoms such as seizures or headache. Intestinal *T. solium* infection (taeniasis) can be eradicated with a single dose of niclosamide.

Medical therapy alone may not be effective for cysts located within the ventricles or spinal cord. Surgical removal of cysts should be considered for patients with cysts in the ventricles, spinal cord, or orbits, and with the racemose form of NCC. Ventricular shunting should be considered when hydrocephalus is present. Expert advice should be sought for patients with racemose, encephalitis, and intraventricular forms of NCC.

CONCLUSION

Infections of the nervous system in international travelers, although uncommon, are increasing in frequency as more people venture through developing countries. For the neurologist confronted with a returning traveler with neurological symptoms, the challenge of efficiently diagnosing and correctly treating a potential CNS infection can be daunting. This chapter examined five potential CNS infections. Through obtaining detailed travel and exposure history, as well as neuroimaging and neurological examination, the neurologist can formulate an initial list of potential etiologies and perform appropriate diagnostic testing. Experts in travel medicine are available in most major medical centers and should be consulted for assistance with diagnosis and treatment.

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KEY POINT

- Over 30 new infections such as Ebola, Nipah virus, and Hantavirus have emerged over the past few decades.
- Travel history, neurological examination, and neuroimaging should guide diagnostic and therapeutic decisions for travelers with “tropical” infections.
- Most travel-related infections can be minimized or prevented by suitable precautions taken before or during travel. Travelers should consult a travel medicine clinic to determine if vaccinations or prophylactic medications are indicated. This consultation should preferably take place 4 to 6 weeks before the journey.
- The key elements of an individual risk assessment include destination, duration and purpose of travel, conditions of accommodation, and health status of the traveler. Special precautions may be necessary for certain high-risk travelers, including infants, pregnant women, elderly persons, disabled persons, and people with immunosuppression or preexisting health problems.
- Dengue is present in virtually every country in the southern hemisphere and is the arboviral infection international travelers are most likely to encounter.
- Neurological dysfunction develops in up to 5% of people with dengue and may manifest as spastic paraparesis, Guillain-Barré syndrome, Bell's palsy, mononeuropathy or polyneuropathy, or seizures.
- Japanese encephalitis is probably the most important viral encephalitis worldwide.
- Approximately 30,000 to 50,000 cases of Japanese encephalitis and 15,000 deaths are reported each year, mostly in children, but fewer than 1 case per year occurs in US civilians or military personnel traveling to or living in Asia.
- In one study of survivors of severe Japanese encephalitis, neurological deficits were common and included quadriplegia (60%), hemiplegia (12%), muscle wasting (25%), and seizures (50%).
- The Centers for Disease Control and Prevention recommends completion of three vaccinations at least 10 days prior to departure for travelers to endemic countries due to the potential risk of a delayed hypersensitivity reaction (angioedema) associated with vaccination.
- Over 1000 cases of malaria occur each year among tourists from the United States.
- *Falciparum* malaria is the most common cause of cerebral malaria.
- Cerebral malaria is characterized by an unarousable state accompanied by parasitemia (most often *P. falciparum*), and diagnosis requires exclusion of

other etiologies, such as hypoglycemia, postictal sedation, or other CNS infection.

- Examination of thick and thin blood smears with Giemsa staining can detect parasitemia and identify malarial species.
- Patients with cerebral malaria who are treated with steroids have a poorer outcome than those who do not receive them; thus steroids should not be administered to patients with cerebral malaria.
- In the United States, wild animals such as raccoons, skunks, bats, and foxes are the most common animal reservoirs of rabies, and domestic animals (ie, dogs and cats) account for less than 10% of infections.
- Recently, several cases of rabies infection occurred in organ transplant recipients.
- Classic rabies presents in either the encephalitic (furious) form with fluctuating consciousness, phobic spasms, and autonomic dysfunction, or the paralytic (dumb) form, which presents with weakness or sensory symptoms in the bitten limb progressing to generalized paralysis; symptoms similar to Guillain-Barré syndrome have also been described.
- Rabies virus antigen detection within nerve cells in the brain or skin biopsy using fluorescent antibody technique is highly specific and sensitive.
- Rabies should be included in the differential diagnosis of undiagnosed encephalopathy in any patient returning from a country where rabies is endemic.
- Neurocysticercosis is perhaps the most common cause of epilepsy in the developing world.
- Two types of infection with *Taenia solium* can occur in humans: (1) taeniasis, an intestinal tapeworm infection caused by eating undercooked pork containing cysticerci (larva); and (2) cysticercosis, an infection caused by ingestion of *T. solium* eggs excreted in the feces of a human with taeniasis.
- Definitive diagnosis of neurocysticercosis can be made if the following are present: (1) histopathological evidence of neurocysticercosis; (2) a scolex within a cystic lesion visualized by CT or MRI; or (3) lesion(s) suggestive of neurocysticercosis by neuroimaging with serological evidence of *T. solium* infection by serum enzyme-linked immunoelectrotransfer blot or CSF enzyme-linked immunoabsorbent assay.
- The sensitivity of serum enzyme-linked immunoabsorbent assay is only 50% in people with a single intraparenchymal CNS lesion.
- Experts agree that most symptomatic neurocysticercosis occurs during the inflammatory response induced by death of the cyst.

- People with neurocysticercosis with homogeneously enhancing or hypodense lesions (active infection) should receive treatment with albendazole or praziquantel; both anthelmintics are cysticidal.
- Treatment of neurocysticercosis has been associated with long-term improvement of seizures and with decrease in number and size of intraparenchymal lesions.
- Medical therapy alone may not be effective for cysts located within the ventricles or spinal cord.
- Through obtaining detailed travel and exposure history, as well as neuroimaging and neurological examination, the neurologist can formulate an initial list of potential etiologies and perform appropriate diagnostic testing. Experts in travel medicine are available in most major medical centers and should be consulted for assistance with diagnosis and treatment.

Case 6-1

A 58-year-old Japanese man who was living in Brazil for several months presented for evaluation after developing anorexia, fever, thrombocytopenia, and rash on the arms and legs. Liver enzymes were initially elevated but normalized over days. One week after onset of illness, he developed sensory changes, progressive paraplegia, and visual loss. CSF showed mildly elevated protein (89 mg/dL) and pleocytosis (21 cells/mm³). ImmunoglobulinM(IgM) antibody to dengue virus was detected in serum. T2-weighted MRI of the spinal cord showed high signal intensity lesions (Figure 6-1A), and T1-weighted MRI with contrast showed enhancement from T7 to T11 (Figure 6-1B and C). MRI of the brain was normal (Yamamoto et al, 2002).

Comment. This patient presented with a prodromal febrile rash, followed by paraplegia in the setting of a mild CSF pleocytosis. As is typical for dengue fever, the brain imaging was normal.

FIGURE 6-1.

Dengue hemorrhagic fever.

From Yamamoto Y, Takasaki T, Yamada K, et al. Acute disseminated encephalomyelitis following dengue fever. *J Infect Chemother* 2002;8:175–177. Reprinted with permission from Springer.

Case 6-2

A 7-year-old boy presented with acute onset of high-grade fever, chills, rigors, and headache. One day later he developed left hemiplegia and left facial weakness without cognitive or sensory changes. Cerebrospinal fluid (CSF) examination revealed 340 cells/mm³, 100% lymphocytes, with protein 114 mg/dL and glucose 66 mg/dL. IgM ELISA for Japanese encephalitis virus revealed titers of 226 units in serum and 223 units in CSF, strongly suggestive of Japanese encephalitis. Three days later he had a generalized tonic-clonic seizure and did not return to his baseline mental state for 10 days. Hemiparesis showed no improvement (Nalini et al, 2003). Axial fluid-attenuated inversion recovery (FLAIR) MRI (Figure 6-2) showed hyperintense foci involving bilateral thalami and small areas of the right frontal and parietal cortices.

Comment. This patient demonstrates a typical presentation of Japanese encephalitis: a young child presenting with prodromal febrile illness, followed by hemiparesis and seizure and a mild lymphocytic pleocytosis.

FIGURE 6-2.

Japanese encephalitis.

From Nalini A, Arunodaya GR, Taly AB, et al. Hemiplegia: an initial manifestation of Japanese encephalitis. *Neurol India* 2003;51:397–398. Copyright © 2003, Neurological Society of India. Reprinted with permission.

Case 6-3

A 30-year-old man returned to France from a 4-week visit in Niger, having taken no prophylactic medications or immunizations. Upon return to France, he reported feeling faint and having headaches and soon thereafter lost consciousness. Blood smear revealed parasitemia with *Plasmodium falciparum*. The patient was treated with intravenous quinine dihydrochloride, and MRI of the brain performed 36 hours after onset of coma showed diffuse abnormalities of the white matter in the centrum semiovale and the splenium of the corpus callosum. The patient regained consciousness, but memory defects, as determined by neuropsychological testing, remained. Follow-up MRI, performed 1 week after onset of neurological symptoms, demonstrated resolution of the abnormalities in the centrum semiovale but only minimal decrease in the size of the lesion of the splenium of the corpus callosum. Five months later his neuropsychological test scores were normal but the corpus callosum was unchanged (Cordoliani et al, 1998).

Comment. This patient demonstrates the typical presentation of cerebral malaria after travel to an area with endemic *P. falciparum* malaria. His MRI findings and improvement after treatment with quinine are also typical.

From Cordoliani YS, Sarrazin JL, Felton D, et al. MR of cerebral malaria. *AJNR Am J Neuroradiol* 1998;19:871-874. Copyright © American Society of Neuroradiology. Reprinted with permission.

Case 6-4

A 23-year-old male tourist was bitten by an aggressive puppy while playing with a small group of dogs on the beach in Agadir, Morocco. The minor wounds healed without complication, and no medical treatment was sought. Four weeks later, the man developed a temperature of 39°C with headache and right arm pain and was hospitalized. On examination he demonstrated hydrophobia, aerophobia, agitation, and increased salivation. Subsequently, he developed generalized tremor, hypotension, and tachycardia and was intubated and transferred to the intensive care unit. Rabies vaccine and human rabies immunoglobulin were administered. Skin biopsy from the nape of the neck, CSF, nasal and pharyngeal swabs, and serum were sent to rabies laboratories in Austria and the United States; skin biopsy and pharyngeal swab were positive for rabies virus by reverse transcription–PCR. Results from fluorescence antibody and immunohistochemical tests of the skin biopsy were also positive, and immunohistochemical investigation of the neck biopsy specimen revealed intracytoplasmic granules. Rabies serum antibody tests performed 4 and 20 days after onset of symptoms were 0.38 U/mL and 52.09 U/mL, respectively. Twenty days postadmission, two different electroencephalograms showed no brain activity, and life support was discontinued (Krause et al, 2005). MRI demonstrated FLAIR signal abnormalities in the left medial temporal lobe (Figure 6-3A), bilateral thalami (Figure 6-3B), and diffusion abnormalities in the posterior frontal lobes (Figure 6-3C) (Burton et al, 2005).

Comment. Although not common in domestic animals in the United States, this case illustrates the increased prevalence of rabies in animals encountered by travelers in the developing world. The patient's presentation with hydrophobia, aerophobia, and increased salivation, followed by onset of autonomic instability, is typical of rabies. Diagnostic test of choice is skin biopsy of the nape of the neck.

FIGURE 6-3.

Rabies.

Burton EC, Burns DK, Opatowsky MJ, et al. Rabies encephalomyelitis: Clinical, neuroradiological, and pathological findings in 4 transplant recipients. *Arch Neurol* 2005;62:873–882. Reprinted with permission.

Case 6-5

A 43-year-old male noted fever and myalgias after returning from a monthlong visit to Colombia and Guatemala. Creatine phosphokinase was elevated, and mild peripheral blood eosinophilia was present. He was diagnosed with mild polymyositis, and his symptoms improved with anti-inflammatory therapy. Two years later he was admitted to a hospital with severe retro-orbital headache and right homonymous hemianopsia. Serum ELISA and immunoblot testing were positive for *T. solium*. Gadolinium-enhanced MRI of the brain showed several intraparenchymal, subarachnoid, and intraventricular cysts (Figure 6-4) with peri-lesional edema (black arrow) and ringlike enhancement (Chatel et al, 1999).

Comment. Although this patient did not develop seizures, his presentation with headaches and focal neurological deficits years after travel to an area with endemic *T. solium* infection is typical for neurocysticercosis, as are the cysts noted on brain imaging.

FIGURE 6-4.

Neurocysticercosis.

Chatel G, Gulletta M, Scolari C, et al. Neurocysticercosis in an Italian traveler to Latin America. *Am J Trop Med Hyg* 1999;60:255–256. Reprinted with permission from the American Society of Tropical Medicine and Hygiene.

Table 6-1

Neurological and Neuroimaging Findings and Diagnostic Testing of Selected Central Nervous System Infections

Infection	Neurological Effects	Neuroimaging Findings	Diagnostic Testing
Japanese encephalitis	Delirium, seizures, axial rigidity, movement disorders, cranial nerve palsies, ataxia, paraplegia and segmental sensory disturbances, acute flaccid paralysis	T2-weighted signal changes in the basal ganglia, substantia nigra, pons, cerebral cortex, or cerebellum	Detection of virus-specific IgM antibodies in the CSF or serum by ELISA, lymphocytic pleocytosis common
Cerebral malaria	Coma, seizures, cranial nerve dysfunction, cognitive dysfunction, postmalaria neurological syndrome	Cerebral edema, multifocal cortical or subcortical lesions that may enhance after gadolinium administration, high-signal intensity on diffusion-weighted imaging, and decreased signal on apparent diffusion coefficient maps	Detection of parasites on thick and thin blood smears with Giemsa staining; serological tests (ParaSight-F and immunochromatographic malaria <i>Plasmodium falciparum</i> test) are available, but false-positive tests are common
Rabies	(1) Encephalitic (furious) form: fluctuating consciousness, phobic spasms, autonomic dysfunction, pharyngeal spasms when offered water (hydrophobia) or exposed to moving air (aerophobia) (2) Paralytic (dumb) form: weakness or sensory symptoms in the bitten limb progressing to generalized paralysis, symptoms similar to Guillain-Barré syndrome Both encephalitic and paralytic forms progress to generalized flaccid paralysis, respiratory and vascular collapse, and coma	Increased T2-weighted or FLAIR signal abnormalities in the brain stem, cortex, subcortex, hippocampus, hypothalamus, and basal ganglia; enhancement of these areas after administration of gadolinium	Rabies virus can be detected in saliva or CSF by culture or reverse transcriptase polymerase chain reaction (PCR); rabies virus antigen detection within nerve cells in the brain or skin biopsy using fluorescent antibody technique is highly specific and sensitive; serum and spinal fluid can be tested for antibodies to rabies virus in people who have not been previously vaccinated; CSF examination may reveal mild lymphocytic pleocytosis
Dengue	Headache and retrobulbar pain; sleeplessness, restlessness, and mood change; seizures; spastic paraparesis; Guillain-Barré syndrome; transverse myelitis; Bell's palsy; mono- or polyneuropathy	Cerebral edema or evidence of encephalitis on T2-weighted and FLAIR sequences	Detection of dengue-specific IgM in serum; fourfold rise in dengue-specific IgG titer (CSF or serum); identification of virus in the CSF by PCR; antibody detection can cross-react with other flaviviruses (eg, Japanese encephalitis virus); CSF typically reveals elevated protein and mild lymphocytic pleocytosis
Neurocysticercosis (<i>Taenia solium</i>)	Seizures, cognitive changes, headache, meningismus, tremor, diplopia	Calcified or enhancing lesions (homogenous or ring-enhancing), large cysts; may see scolex on magnetic resonance imaging	Detection of anti- <i>T. solium</i> IgG/IgM antibodies in serum or CSF; CSF testing less sensitive; patients with solitary lesion often have negative serology

IgM = immunoglobulin M; CSF = cerebrospinal fluid; ELISA = enzyme-linked immunoabsorbent assay; FLAIR = fluid-attenuated inversion recovery; IgG = immunoglobulin G.

Table 6-2

Treatment and Immunization

Infection	Chemoprophylaxis Available	Treatment	Vaccine Available	Note
Japanese encephalitis	No	Supportive therapy	Yes	Only domestic pigs and wild birds are carriers of the Japanese encephalitis virus
Malaria	Yes	For suspected cerebral malaria due to chloroquine-resistant or unknown-resistance <i>Plasmodium</i> , treatment should include intravenous (IV) quinidine: 10 mg/kg IV loading dose in normal saline over 1 to 2 hours; then 0.02 mg/kg/min until patient can swallow; then quinine tablets, 30 mg/kg for 3 to 7 days	No	Use of steroids and prophylactic anticonvulsants in patients with cerebral malaria have been associated with worse outcome; treat elevated intracranial pressure with mannitol
Rabies	No	Treatment of a person exposed to rabies varies by vaccination status; if previously vaccinated, the person should receive rabies vaccine intramuscularly in the deltoid area on days 0 and 3; if not previously vaccinated, vaccine as well as rabies immune globulin (20 IU/kg infiltrated into or around the wound and intramuscularly) should be administered	Yes	Pre-exposure if at high risk; protection lasts 2 years
Dengue	No	Supportive therapy	No	To manage pain and fever in patients with dengue infection acetaminophen should be used rather than aspirin as anticoagulant effects of aspirin may aggravate bleeding
Neurocysticercosis	No	Albendazole 15 mg/kg/d in bid dosing (maximum 400 mg bid) for 8 to 30 days, or praziquantel 50 mg/kg/d in tid dosing for 30 days	No	Steroids should be considered when marked edema, multiple or meningeal cysts are present

For more information, see <http://www.cdc.gov/travEI/>

For dosing, consult Abramowicz M, ed. Drugs for parasitic infections. Medical Letter: on drugs and therapeutics, [online] 2004 [accessed December 6, 2005]. Available from: <http://www.themedicalletter.com>

bid = twice a day; tid = three times a day.

Table 6-3**Resources****► Web Site Resources**

World Health Organization (WHO)	http://www.who.org
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov/travel
US Department of State	http://www.travel.state.gov
International Society of Travel Medicine	http://www.istm.org
Royal Society of Tropical Medicine and Hygiene	http://www.rstmh.org
American Society of Tropical Medicine and Hygiene	http://www.astmh.org
Travax EnCompass	http://www.travax.com
Mortality and Morbidity Weekly Report (MMWR)	http://www.cdc.gov/mmwr/
Emerging Infectious Diseases Journal (EIJ)	http://www.cdc.gov/ncidod/eid/
Program for Monitoring Emerging Diseases (ProMED)	http://www.fas.org/promed

► Books

Travelers' Health: Yellow Book; Health Information for International Travel (Available from: <http://www.cdc.gov/travel/yb/> Accessed December 1, 2005)

Travelers' Health: Summary of Health Information for International Travel (formerly "The Blue Sheet") (Available from: <http://www.cdc.gov/travel/blusheet.htm>. Accessed December 1, 2005)

The Green Sheet; Centers for Disease Control and Prevention's inspection scores of specific cruise ships (Available from: <http://www.cdc.gov/travel/cruiships.htm>. Accessed December 1, 2005)

International Travel and Health; World Health Organization (Available from: <http://www.who.int/ith/en/>. Accessed December 1, 2005)