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Neurologic Aspects of Infections in International Travelers

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Abstract

Background—As international travel for business and pleasure becomes part of contemporary lifestyle, the clinician today is confronted with an increasing number of travelers returning ill with unfamiliar syndromes. The physician will encounter a myriad of patients with exotic infections, emerging infectious diseases, or resurgent Old-World infections.

Review Summary—This review article will discuss salient points of important infectious diseases associated with overseas travel, provide a syndromic approach to the traveler who returns with neurologic manifestations, and list resources for additional diagnostic, therapeutic, and preventive information.

Conclusions—As many of infections acquired in other countries can directly or indirectly affect the nervous system, the care of the ill traveler often falls into the hands of neurologists. The contemporary neurologist should therefore be knowledgeable of the clinical manifestations, potential complications, and appropriate management of region-specific infections.

Keywords

infection; nervous system; travel

I should like to rise and go,

Where the golden apples grow;

Where below another sky,

Parrot islands anchored lie...

Robert Louis Stevenson (1850–1894)

(A Child's Garden of Verses and Underwoods)

A similar desire was probably stirred in the human soul since medieval ages, leading people to foreign lands in search of adventure, wealth, power, and religion.¹ Marco Polo's travel to Asia, Sir Francis Drake's seafaring trip around the world, and Chaucer's *Canterbury Tales* exemplify our aspirations and fascination with overseas travel.^{2–4} Although the motivations for travel may have changed over the centuries, the number of international travelers has significantly increased and continues to grow.⁵ With the increasing availability of airplane travel, industrialization of tourism, and web-based marketing, international travel has become accessible and convenient to the masses. In 2000, over 50 million people from Europe and North America traveled to tropical countries for professional, social, recreational, and humanitarian purposes.⁶

The unfortunate traveler may succumb to an exotic infection during the trip. Early examples of travel-related mishaps include Columbus and his crew returning to Spain with syphilis and pilgrims falling prey to malaria and plague.^{7,8} Foreign travel has become safer in modern days, but the paradigm of travel-related infections has shifted and now presents a public health problem of increasing importance.

Factors contributing to the changing spectrum of neurologic infections in travelers include increasing number of travelers, newly emergent infections, and appearance of drug-resistant organisms. With the increasing popularity of group tours, wildlife expeditions, and adventure sports, more travelers are exposed to environments containing endemic tropical infections (Table 1).⁹ Over 30 new infections such as Ebola, variant Creutzfeldt-Jakob disease, Nipah virus, and hantavirus have emerged over the past few decades.¹⁰ In addition, changes in ecosystems have contributed to the spread of some tropical infections to different continents, most notably West Nile virus (WNV), dengue and Japanese encephalitis (JE).^{11,12} Finally, new strains and drug-resistant forms of “Old World diseases” like malaria, tuberculosis, and meningococcal diseases have reemerged. Thus, travel-related infectious diseases pose a major threat not only to the individual traveler but potentially to the population at large.

This review article provides a syndromic approach to the evaluation of a traveler who returns ill with neurologic symptoms or signs. A list of potential etiologies can be formulated through questioning the ill traveler about countries visited and potential food or vector exposures (Tables 2 and 3). Neurologic manifestations, key systemic characteristics, potential complications, and prognostic factors of some common infections are discussed in detail. In addition, recommendations for preventive measures and information on vaccines are provided (Table 4). Finally, web-based resources and organizations where additional information can be obtained or to whom infectious diseases can be reported are listed at the end of the article (Table 5).

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The international traveler who returns with fever, headache, neck pain, and photophobia must be promptly evaluated for potential meningitis or encephalitis. Meningoencephalitis is a common neurologic manifestation, and timely evaluation and treatment may prevent devastating neurologic complications or death.

ARBOVIRAL ENCEPHALITIDES

Arboviral encephalitides are caused by viruses transmitted by the bite of a blood-feeding arthropod vector, such as the mosquito, tick, or flea. Transmission occurs most frequently between June and September, when arthropods are most active. There are more than 500 known arboviruses in 4 viral families—Flaviviridae, Togaviridae, Bunyaviridae, Orbiviridae—among which at least 15 can cause viral encephalitis.¹³ Arboviruses have an alarming ability to spread to new geographical locations and cause substantial outbreaks and thus play an important role in emerging infectious disease.¹⁴

There are 4 main arboviral encephalitides in the United States: Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis, and La Crosse encephalitis. Venezuelan equine encephalitis, JE, and tick-borne encephalitis (TBE) are more prevalent in other parts of the world. WNV, previously foreign to the United States, was first identified in the eastern United States in 1999, and has now spread over most of North America.¹⁵

Some arboviruses invade the nervous system and cause meningitis, encephalitis, or myelitis.

Arboviral infections in humans are usually mild and self-limited. Patients typically present with nonspecific flulike symptoms: fever, headache, eye pain, back pain, malaise, myalgias, and rash. Some arboviruses invade the nervous system and cause meningitis, encephalitis, or myelitis. In severe cases, patients may develop meningismus, change in mental status, coma, hemiparesis, aphasia, ataxia, pyramidal signs, cranial nerve deficits (most often third and seventh cranial nerves), myoclonus, tremor, or partial seizures. Fulminant infection commonly results in permanent neurologic deficit or death.¹³ Arboviral encephalitis can be diagnosed by detection of virus-specific nucleic acid in the cerebrospinal fluid (CSF) with polymerase chain reaction (PCR) assay, of virus-specific antibody in CSF by ELISA (enzyme-linked immunosorbent assay), or by 4-fold rise in virus-specific antibody titer in serum. CSF pleocytosis is common, and neuroimaging studies may reveal focal areas of enhancement consistent with encephalitis.

Treatment is usually supportive. Arboviral encephalitis is best prevented by personal protective measures and public health measures to reduce exposure to infected mosquitoes. There are no commercially available human vaccines for the 4 arboviral infections found in the United States, but vaccines for JE and TBE are available.

Japanese Encephalitis (JE)

Although considered by many in the West to be a rare and exotic infection, JE 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 the infection is enzootic and occurs throughout the year. Approximately 50,000 infections and 15,000 deaths are reported each year, mostly in children, but actual numbers are probably higher.⁶ The risk of infection among travelers to South East Asia has been estimated between 1 in 5000 to 20,000 travelers per week.¹⁶

JE is caused by a flavivirus maintained in a life cycle involving mosquitoes and aquatic birds. The virus is transmitted to humans by *Culex* mosquitoes, primarily *C. tritaeniorhynchus*, which breed in rice fields. In residential environments, pigs are the main amplifying host of JE virus.

Clinical Manifestations

The incubation period of JE is 5 to 14 days. The majority of infections are asymptomatic, with only 1 of every 30 to 300 infected people developing symptoms.⁶ Mild infections produce a flulike illness that resolves within 5 to 7 days. More serious infections cause meningoencephalitis or other CNS manifestations. Patients initially present with fever, headache, and vomiting, then rapidly develop decreasing level of consciousness, seizures, and death. CNS complications during the acute illness include delirium, seizures, axial rigidity, extrapyramidal signs, cranial nerve palsies, ataxia, paraplegia, and segmental sensory disturbances.¹⁷ A new variant of the disease predominantly affects the spinal cord, causing acute flaccid paralysis.¹⁸

Diagnosis

Lymphocytic pleocytosis is common in CSF of patients with JE. The infection is confirmed by detection of virus-specific antibodies in the CSF or serum by ELISA.¹⁹ Magnetic resonance imaging (MRI) of the brain often reveals characteristic hemorrhagic lesions in the bilateral thalamus.²⁰ Other common neuroimaging abnormalities include T2-weighted signal changes in the basal ganglia, substantia nigra, pons, cerebral cortex, or cerebellum.^{20,21}

Treatment

JE is treated with conservative management. The mortality rate in most outbreaks is less than 10% but in children can exceed 30%.^{15,22} Neurologic sequelae occur in up to 30% of patients who survive severe infection.²³ In one study of survivors of severe JE, neurologic deficits were common and included quadriplegia (60%), hemiplegia (12%), muscle wasting (25%), and seizures (50%).²⁰ 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.²¹ A formalin-inactivated vaccine prepared in mice is used widely in Japan, China, India, Korea, Taiwan, and Thailand.⁶ This vaccine is also available in the United States for travelers to endemic countries.²⁴ A massive vaccination campaign against JE financed by the Gates Foundation will soon be initiated in Southeast Asia. Due to the potential risk of a delayed hypersensitivity reaction (angioedema) associated with vaccination, the CDC recommends travelers obtain the vaccination series at least 10 days prior to departure.

Dengue Hemorrhagic Fever (DHF)

Dengue is present in virtually every country in the southern hemisphere and is the arboviral infection international travelers are most likely to encounter.²⁵ Dengue affects 100 million people worldwide each year and 2.5 billion people—two fifths of the world's population—are at risk for contracting infection.^{26,27}

Dengue virus is a flavivirus transmitted by the bite of *Aedes aegypti* or *A. albopictus* mosquito. There are 4 dengue virus serotypes,¹⁻⁴ all of which have been associated with neurologic disease.

Dengue is present in virtually every country in the southern hemisphere and is the arboviral infection international travelers are most likely to encounter.

Clinical Manifestations

Symptoms usually develop 4 to 7 days after the mosquito bite.²⁸ Most cases present with dengue fever, also known as “break-bone fever,” a self-limited influenza-like illness with high fever, headache, retrobulbar pain, and myalgias. A more severe illness, DHF, 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.²⁶

Separate from the above clinical presentations, dengue infection can also present with 3 distinct neurologic entities:

1. *Acute nonspecific neurologic symptoms:* During acute dengue infection, headache and retrobulbar pain occur in most people.²⁸ In addition, sleeplessness, restlessness, and mood change are common.
2. *Acute encephalitic or focal neurologic symptoms:* Neurologic dysfunction occurs in up to 5% of infected people and may manifest as spastic paraparesis, Guillain-Barré syndrome, Bell palsy, mono- or polyneuropathy, or seizures.^{29,30} Seizures occur in up to 16% of children with primary dengue infection.³¹ Encephalitis occurs infrequently, except in children living in Asia, and is more likely to occur during the viremic period.³² In one study, 18% of children hospitalized in Thailand with an encephalitis-like illness had dengue infection.³³
3. *Postinfectious neurologic complications:* Postinfectious complications are more common in adults and may include transverse myelitis, cranial or peripheral nerve

palsies.^{30,34} The incidence of permanent neurologic dysfunction following dengue infection is unknown.

Spastic paraparesis, generalized convulsions, and alteration in level of consciousness have been reported in association with dengue type 3 infection, and convulsions and coma have been reported with dengue type 2 infection.³⁵

Diagnosis

Analysis of CSF reveals elevated protein and mild lymphocytic pleocytosis.^{30-32,36} Confirmatory diagnosis is made by the detection of dengue-specific IgM in serum, a 4-fold rise in dengue-specific IgG titer (CSF or serum) or identification of virus in the CSF by PCR.^{36,37} Computed tomography (CT) or MRI may reveal cerebral edema or evidence of encephalitis on T2 and FLAIR sequences.^{32,36,38}

Treatment

Treatment is supportive; severe cases require intensive care. The case fatality rate varies by country from less than 1% to over 20%.²⁶ In one review of 168 cases of dengue-related encephalopathy with known outcomes, the mortality rate was 58%; of the remaining 42%, all but 4 had complete recovery.³⁹ 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.⁴⁰

Tick-Borne Encephalitis (TBE)

TBE causes over 10,000 infections annually in Europe and Asia.⁴¹ It is most commonly caused by 1 of 3 flaviviruses: Far Eastern (also known as Russian spring-summer encephalitis), Western European (also known as Central European encephalitis) or Siberian.⁴² The majority of TBE infections are transmitted by the bite of an infected *Ixodes* tick, but the infection has also been transmitted by ingestion of unpasteurized cow or goat milk.⁴³ The highest incidence of human infection occurs in spring and summer during peak tick feeding season.⁴¹

Clinical Manifestations

Symptoms typically start after an incubation period of 7 to 14 days. Patients may present with an influenza-like febrile illness, meningitis, meningoencephalitis, a polioliike illness, polyradiculoneuritis, or chronic infection.⁴⁴ Clinical presentation and outcome vary by geographic region.⁴¹ In Siberia, 80% of cases recover without residual deficits, but in far eastern Russia, disability and fatality rates run as high as 60%.^{45,46} Residual neurologic complications include hemiplegia, limb paralysis, mono- or polyneuropathy, Parkinsonism, seizure disorder, dementia, and progressive muscle atrophy.^{41,47,48}

Diagnosis and Treatment

The diagnosis of TBE is made by viral isolation or demonstration of TBE-specific IgM or IgG antibodies in serum or CSF by ELISA.⁴⁹ Treatment is supportive. Risk of TBE infection can be reduced by avoiding consumption of unpasteurized dairy products and by using tick repellents during extended outdoor activities. An inactivated TBE vaccine is currently available in Europe and Russia. The vaccine is recommended for individuals who travel through endemic areas during warm weather months.^{15,50}

West Nile Virus (WNV) Encephalitis

WNV encephalitis is the emerging viral encephalitis of increasing importance in the United States. First isolated in the West Nile Province of Uganda in 1937, WNV is endemic in Europe, Russia, and Africa.⁵¹ Several epidemics have occurred in Israel, Europe, and South Africa

since the 1950s.^{23,52,53} WNV is an epizootic flavivirus infection affecting birds and a wide range of vertebrate species.⁵⁴ It is transmitted principally by *Culex* mosquitoes but can also be transmitted by *Aedes* and *Anopheles* species.⁵⁵ Year-round transmission occurs even in the absence of outbreaks.⁵⁴

The first outbreak of WNV encephalitis occurred in New York in 1999 and has rapidly spread across the country to affect 46 states.^{56,57} Although it is not certain how WNV was introduced to the United States, experts speculate that it may have been introduced through international travel.⁵⁸ Since 1999, there have been 15,889 human infections reported in the United States through September 2004, 622 of which were fatal.⁵⁹

Clinical Manifestations

Most WNV infections are mild. Incubation period is 3 to 14 days, and symptoms last 3 to 6 days.⁵⁴ Approximately 20% of infected individuals develop a mild infection called “West Nile fever,” consisting of malaise, anorexia, nausea, eye pain, headache, myalgia, and rash.⁶⁰ Half of infected patients develop a nonpruritic, maculopapular rash over the trunk and arms. Approximately 1 in 150 infections develop encephalitis, meningitis, or WNV poliomyelitis.^{56,61,62} Weakness, often flaccid and asymmetric, occurs in over half of these patients; other symptoms include fever, change in mental status, myelitis, optic neuritis, polyradiculitis, seizures, ataxia, extrapyramidal dysfunction, and cranial nerve abnormalities.^{54,57,63} Encephalitis is more common than meningitis; both are more common than WNV poliomyelitis.⁶⁰ In a study of patients with neurologic manifestations, 52% had meningoencephalitis, 33% meningitis, 10% encephalitis, and 5% had polyneuropathy.²³

Diagnosis

Patients with WNV infection involving the nervous system often have peripheral leukocytosis, lymphopenia, anemia, and hyponatremia. Common CSF abnormalities include elevated protein and lymphocytic pleocytosis.^{54,57,60} Definitive diagnosis of WNV infection of the CNS is made by detection of WNV in the CSF by PCR assay, of virus-specific IgM in the CSF, or by 4-fold increase in virus-specific IgG titers between acute and convalescent serum drawn 2 or more weeks apart.⁶⁴ Unfortunately, the PCR assay is relatively insensitive, and false-positive results can occur in patients recently vaccinated for JE or yellow fever.⁶⁵ Neuroimaging studies may reveal leptomeningeal enhancement.³⁷

Treatment

Treatment is supportive, and for severe disease usually includes hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections.^{13,54} Ribavirin in high doses and interferon α -2b are effective in vitro but have not proven effective for human infection. Other medications, such as steroids, anticonvulsants, osmotic agents or Israeli IVIg have not yet been proven effective for treatment of WNV encephalitis.^{66,67} There is a 10% fatality rate with WNV infection, 70% occurring in patients with neuroinvasive disease.^{60,64} Older age is associated with worse outcome.¹³

WNV encephalitis is a reportable arboviral encephalitis and should be suspected in a traveler with unexplained meningitis, encephalitis, or myelitis, especially if accompanied by a flaccid paresis.^{63,66,67} Timely identification of persons with acute WNV or other arboviral infection would have significant public health implications, and rapid response could reduce additional reservoirs of infectious mosquitoes.

VIRAL HEMORRHAGIC FEVERS (VHF) AND OTHER VIRAL INFECTIONS AFFECTING THE NERVOUS SYSTEM

VHF (eg, yellow fever, Ebola, Lassa, Marburg) are enzootic infections endemic in Asia, South America, and Africa and are transmitted in rodent excreta or biologic fluids from infected individuals. Most VHF are transmitted by mosquitoes, rodents or ticks, but Ebola, Lassa, Marburg, and Crimean-Congo HF are spread by direct contact.⁶ VHF poses little risk to the international traveler unless travel includes exposure to urban areas, cave exploring, monkeys, or rat urine. VHF typically produces nonspecific symptoms within 3 weeks of exposure, and hemorrhage may not be present initially. Severely ill patients may also develop encephalitis, seizures, delirium or coma.⁶⁸⁻⁷⁰ Several cases of Lassa fever have been reported in international travelers.⁷¹ Evaluation of a patient with suspected VHF should include testing to exclude malaria. Diagnostic specimens should be properly handled, labeled, and shipped to a diagnostic laboratory with biosafety level 4 facilities. Diagnosis of VHF can be confirmed by viral isolation, PCR assay, or identification of virus-specific antigens or antibodies in CSF or serum. Treatment is usually supportive, but ribavirin is effective for some VHF and should be administered if VHF is suspected.⁷²

MENINGOCOCCAL MENINGITIS

Despite widespread availability of vaccines and antibiotics, bacterial meningitis remains a threat worldwide.⁷³ Meningococcal meningitis is probably the most important cause of bacterial meningitis, given its high rates of fatality and high transmissibility.⁷⁴ Of the 13 serogroups of *Neisseria meningitidis*, only 5 groups, A, B, C, Y, and W-135, are clinically important. Serotypes B and C are prevalent in Europe and the Americas, whereas serotypes A and C are associated with major epidemics in Asia and Africa.⁷⁵⁻⁷⁷ Serotype W-135 caused an outbreak among Hajj pilgrims in 2000.⁷⁸ Major African epidemics affect up to 1000 per 100,000 inhabitants, and 65% of total meningitis cases are found in Ethiopia, Nigeria, and Burkina Faso, also known as the “meningitis belt.”⁷⁹ Although sporadic cases occur worldwide, risk is highest for travelers visiting the meningitis belt or exposed to crowded areas. Humans are the only reservoir of meningococcal disease, and 10% of the population are asymptomatic nasal carriers.⁷³ The infection is transmitted by direct contact or droplet spread. Susceptibility to meningococcal infection is highest during infancy and early adulthood.⁸⁰

Clinical Manifestations

The incubation period after exposure usually lasts from days to weeks. Meningitis occurs in 50% of infections and typically presents with a sudden onset of fever, severe headache, photophobia, neck stiffness, and altered mental status.⁸⁰ Meningococcemia occurs in 15% to 20% of complicated infections and causes a characteristic hemorrhagic skin rash, circulatory collapse, adrenal hemorrhage, and multiorgan failure.^{80,81} Even with appropriate antimicrobial therapy and optimal medical care, the case fatality rate is 12% and rises to 40% in cases of meningococcal sepsis.⁷³ Permanent neurologic disabilities develop in 11% to 19% of survivors.⁸²

Treatment of meningococcal meningitis is penicillin G 4 million units IV every 4 hours for 5 to 7 days.⁷³ Patients allergic to penicillin can be treated with chloramphenicol 50 mg/kg IV every 6 hours. Vaccination is recommended for travelers to Mecca, Saudi Arabia during the annual Hajj, and to countries with epidemic meningococcal disease caused by serogroups A, C, Y, and W135 during the dry season.⁸³ The vaccine is effective against meningococcal infection for at least 3 years. The CDC currently does not recommend chemoprophylaxis for returned travelers.

HAEMOPHILUS INFLUENZA MENINGITIS

Few countries in the world routinely use *Haemophilus influenza* type b (Hib) vaccine, so Hib meningitis remains common in many parts of the world. Infants and children under 5 years of age are most susceptible to Hib meningitis, especially infants less than 6 months. The best prevention against Hib meningitis is complete vaccination before travel. For infants too young for vaccination, antibiotic treatment is indicated. At times, prophylactic antibiotics are indicated for those who are exposed to patients with Hib infection. Treatment of *H. influenza* meningitis is ampicillin (300 – 400 mg/kg/d in 4 to 6 divided doses) for susceptible strains or ceftriaxone (75 mg/kg/d loading dose, then 100 mg/kg/d) for 7 to 10 days.^{84,85}

EOSINOPHILIC MENINGITIS (EM)

EM is typically associated with parasitic infection of the CNS and is characterized by the presence of 10 or more eosinophils per cubic millimeter or pleocytosis with 10% or more eosinophils in the CSF.⁸⁶⁻⁸⁸ A wide variety of parasites can produce CNS infections, including *Trypanosoma cruzi* (Chagas disease), *Taenia solium* (neurocysticercosis), *Schistosoma* spp. (schistosomiasis), *Strongyloides stercoralis* (strongyloidiasis), *Echinococcus* spp. (echinococcosis), *Paragonimus westermani* (paragonimiasis), *Toxocara canis* (toxocariasis), *Trichinella spiralis* (trichinosis), and *Entamoeba histolytica* (amoebiasis).⁸⁹ Parasitic CNS infection is most common in the tropics and subtropics and in the United States is most commonly encountered in vacationers returning from endemic regions.⁹⁰ Hosts of these parasitic infections are varied, ranging from snails to vertebrate animals.^{90,91} Infection can be transmitted by ingestion (cysticercosis, angiostrongyliasis) or direct contact with skin or mucous membrane (strongyloidiasis).⁸⁹ Although the life cycle of most parasites within the human host is usually self-limited, ensuing host inflammatory response often produces a diverse clinical spectrum of acute and chronic neurologic manifestations. Most infected travelers develop fever and signs of meningitis or meningoencephalitis at some point during the illness. More serious infections may develop necrotizing hemorrhagic meningoencephalitis, cerebral infarcts, or subarachnoid hemorrhage.⁹²⁻⁹⁴ The CSF profile may include elevated protein and eosinophilic pleocytosis.^{89,95} Peripheral blood smear and stool examination for parasitic larva or eggs may be useful but are often negative.⁸⁹ In some infections, direct examination of CSF may reveal the organism, including larvae of *A. cantonensis*, the procyclic form of African trypanosomes, trophozoites, free-living amoeba or *Entamoeba histolytica*, microfilariae, cysts, or larvae of *Trichinella spiralis*.⁸⁹ Neurologic and neuroimaging findings, as well as recommended treatments for some common parasitic CNS infections, are listed in Table 6.

Eosinophilic meningitis is typically associated with parasitic infection of the CNS.

ASEPTIC MENINGITIS

The international traveler may also return with aseptic meningitis: symptoms of meningitis, CSF pleocytosis, and no identifiable causal pathogen. Viruses are believed to cause the majority of aseptic meningitides.⁹⁶ The diagnosis of aseptic meningitis requires the exclusion of other potential infections. As most cases of aseptic meningitis are self-limited, further evaluation is warranted if the course is protracted.

CEREBRAL MALARIA

Malaria, also known as “black-water fever,” is a febrile illness common in travelers to Africa, Central and South America, and Southeast Asia. Of the 125 million people from nonendemic countries who travel through malaria-endemic countries each year, 10,000 to 30,000 will

contract malaria.^{97,98} Over 1000 cases of malaria occur each year among tourists from the United States.

Malaria is caused by *Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae* and is transmitted by mosquito bite. Approximately 90% of the falciparum malaria is acquired in sub-Saharan Africa, and 70% of vivax malaria is acquired in Latin America and Asia.⁹⁸ Falciparum malaria is the most important species as it can cause cerebral malaria and carries a mortality rate of 20% to 50%.⁹⁹

Cerebral malaria is defined as an unarousable state accompanied by presence of asexual parasitemia (most often *P. falciparum*) with exclusion of other etiologies, such as hypoglycemia, postictal sedation, or other CNS infection.⁹⁷ Cerebral malaria most often occurs in pregnant women, children, nonimmune populations, and people taking inadequate chemoprophylaxis.

Clinical Manifestations

Initial symptoms include intermittent fever with chills, headache, nausea, vomiting, abdominal pain, and myalgias followed by stupor and coma. Cranial nerve dysfunction, such as horizontal or vertical nystagmus, ocular bobbing, or sixth nerve palsy is occasionally present. Seizures occur in 20% to 50% of patients with cerebral malaria and are typically focal and recurrent. Coma may develop precipitously or subacutely following a generalized seizure and typically lasts 1 to 3 days. The incidence of epilepsy following cerebral malaria is unknown. Patients who recover from severe malaria can have a self-limited acute confusional state in the setting of aparasitemia called postmalarial neurologic syndrome; this syndrome is more common in people treated with mefloquine.¹⁰⁰

Diagnosis

Examination of thick and thin blood smears with Giemsa staining can detect parasitemia and identify malarial species. Serologic tests (ParaSight-F and Immunochromatographic Malaria *P. falciparum* test) are available but false-positive tests are common.¹⁰¹ CT may demonstrate cerebral edema during the agonal stages of cerebral malaria.¹⁰² MRI may reveal brain enlargement without edema.¹⁰³ Transtentorial herniation is a common CT or MRI finding in fatal cases.

Treatment

The choice of treatment should be guided by *Plasmodium* species prevalent in the region where infection was acquired. Chloroquine-resistant *P. falciparum* is present in Southeast Asia, the Amazon region of South America, and certain areas of sub-Saharan Africa. In this situation, quinine with doxycycline, mefloquine, or newer antimalarial drugs (halofantrine or artemisinin derivatives) can be used.¹⁰⁴ For the traveler with suspected cerebral malaria due to chloroquine-resistant or unknown-resistance *Plasmodium*, initial treatment should include intravenous quinine: 20 mg/kg IV loading dose diluted in 10 mL isotonic fluid per kilogram over 4 hours; then 8 hours later, 10 mg/kg over 4 hours repeated every 8 hours until the patient can swallow, then quinine tablets, 10 mg/kg QID for 7 days, or a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine, 75 mg pyrimethamine). Dosing of IV quinine for children should be given every 12 hours.^{99,105} Concomitant treatment with steroids may be associated with worse outcome.^{106,107} Treatment of elevated intracranial pressure with mannitol has been associated with improved outcome.¹⁰⁸ Prophylactic anticonvulsants in patients with cerebral malaria has been associated with worse outcome.¹⁰⁹ Poor prognosis is associated with prolonged seizures, presence of retinal hemorrhages, coma, presence of hypoattenuation on CT imaging of the brain, hypoglycemia, and anemia.^{99,110} Children who develop spastic quadriplegia or vegetative

state usually die. Residual cognitive, behavioral, and language deficits occur, but the incidence is unknown.¹¹¹ Neurologic deficits may be transient or permanent. Prevention of cerebral malaria requires prevention of malaria, including eradication of mosquitoes, personal protective measures, and chemoprophylaxis with mefloquine, chloroquine, or doxycycline. Antimalarial vaccines have unproven efficacy.

ENTERIC FEVER

A disease of antiquity, enteric fever or typhoid fever, is an acute life-threatening infection associated with poor sanitary conditions. Caused by *Salmonella typhi* or *S. paratyphi*, enteric fever is spread by fecal-oral route. Typhoid fever should be suspected in any traveler returning with fever, headache, and delirium with gastrointestinal symptoms (abdominal pain, constipation, or diarrhea), relative bradycardia, characteristic petechial skin rash (rose spots), and splenomegaly. Neuropsychiatric manifestations occur in 50% of patients with typhoid fever and may include confusional state, delirium, coma, generalized myoclonus, parkinsonian rigidity, or psychosis.¹¹² Confirmatory diagnosis is made by culture of blood, bone marrow aspirate, or stool. Identification of a 4-fold rise in antibody titers is also diagnostic. Treatment should include ciprofloxacin (400 mg IV BID), ofloxacin (200 mg BID IV; 10 mg/kg/d for children), or ceftriaxone (2–3 g/day IV) for 7 to 14 days.¹¹³ Typhoid vaccine administered orally or intramuscularly may provide partial coverage against infection in travelers to endemic areas. Vaccination must be readministered every 2 to 5 years.

RABIES

Rabies is an acute, fatal encephalomyelitis caused by Rhabdoviridae. Highly endemic in parts of Africa, Asia, and Central and South America, rabies is almost always transmitted by an infected animal bite. Infected people first develop fever, headache, and paresthesias, followed by paralysis (20%), hydrophobia (80%), delirium, psychosis, coma, and death.¹¹⁴ 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. Diagnosis of rabies often relies on clinical and epidemiological findings. Confirmatory diagnosis is made by PCR assay of skin or saliva, but a negative result does not exclude the diagnosis. Rapid molecular detection and viral typing is essential for early diagnosis and can decrease the number of unnecessary exposures to infected patients. Pre-exposure vaccination is recommended for travelers who anticipate prolonged stays in rural areas with high levels of endemic rabies, as well as for cave explorers (spelunkers). Rabies should be included in the differential diagnosis of undiagnosed encephalopathy in any patient returning from a country with endemic rabies.¹¹⁵

SEIZURES

Seizures are common among international travelers; the differential diagnosis should include the typical causes of epilepsy, but seizures occurring in the setting of a febrile illness or new neurologic deficit should suggest potential CNS infection. Worldwide, neurocysticercosis and schistosomiasis are the most common causes of epilepsy. Seizures occur as the initial symptom in 46% of patients with JE, and 16% have multiple focal or generalized seizures.¹¹⁶ More than 50% of children with DHF who develop neurologic manifestations have seizures.²⁹ In an African study, 62% to 87% of children with cerebral malaria presented with seizures, 28% of whom were in status epilepticus.¹¹⁷ Parasitic CNS infections caused by cysticercosis, strongyloidiasis, ascariasis, and schistosomiasis may manifest with seizures as the primary presentation. Many conditions other than CNS infection can also cause seizures. Dehydration, heat exhaustion, toxins, and high-altitude cerebral edema also produce seizures but are usually self-limited and resolve after correction of the underlying cause.

PARALYTIC ILLNESSES

Poliomyelitis, arboviral myelitis, Guillain-Barré syndrome, and spinal cord infection should be included in the differential diagnosis of paralytic illness in an international traveler. Despite the successes of the WHO global polio eradication campaign, polio remains a threat to the international traveler visiting endemic areas.^{79,118} Clusters of cases still occur in South Asia and central and West Africa. Polio is transmitted by fecal-oral route, and infected individuals may present with meningitis or asymmetric flaccid paralysis. Travelers to endemic areas are advised to receive primary vaccination or a booster dose if vaccination was received more than 10 years prior to travel.¹¹⁹

Arboviral encephalitis can also involve the spinal cord and produce paralytic disease. WNV infection is an emerging cause of myelitis and flaccid paralysis. *Alphavirus*, *Flavivirus*, *Bunyavirus*, and *Phlebovirus* infections are also common causes of paralytic illness. Gastroenteritis due to *Campylobacter jejuni* is associated with Guillain-Barré syndrome and typically produces an acute ascending paralysis with areflexia. Paralytic shellfish poisoning may also cause acute motor weakness. After eating infected shellfish, affected individuals initially develop mouth tingling and weakness of limbs. The illness is usually self-limited, but in severe cases involvement of the diaphragm can lead to respiratory compromise and death.

Focal infections of the spine may also produce spinal cord compression and paralysis. Tuberculous Pott spine is common in developing countries. Parasitic infections of the spinal cord due to cysticercosis, schistosomiasis, and echinococcosis may also present with paralytic disease.¹²⁰⁻¹²²

Polio remains a threat to the international traveler visiting endemic areas.

BEHAVIORAL CHANGES

Many illnesses affecting international travelers can produce mental status or behavioral changes. During the acute phase, any systemic or CNS infection can cause delirium (typhoid psychosis, cerebral malaria). Parasitic CNS infections can also manifest with behavioral changes, depending on the location of the lesion. Degenerative infections such as variant Creutzfeldt-Jakob disease may present with dementia or psychosis. In addition, toxins, high-altitude cerebral edema, drugs, and psychiatric illness can also produce behavioral changes and psychosis mimicking CNS infections.

CONCLUSION

The number of international travelers will continue to increase as faster airplanes are developed and as we continue to live the bourgeois-bohemian lifestyle.¹²³ The risk of CNS infection in returning travelers is also likely to increase. How large is the problem and what is the impact on health care and the society? Out of the 500 million people who traveled overseas in year 2000, over 50% became ill but only 1% to 5% sought medical attention.^{124,125} In an Australian study, only 1% of travelers presenting with a febrile illness were diagnosed with meningitis and encephalitis.¹²⁶ Over 1000 travelers return to the United States yearly with malaria, but the percentage of those with CNS involvement has not been documented. The number of travelers returning with CNS infection is likely to be underestimated due to inadequate reporting and lack of case ascertainment. With increasing travel by people with immunosuppression due to human immunodeficiency virus (HIV), organ transplant, or malignancy, the spectrum and incidence of “tropical” infections will likely expand and include atypical or severe infection.

Most travel-related infections can be minimized by suitable precautions taken before, during, or after travel. Advance planning, appropriate preventive measures, and careful precautions can substantially reduce the risk of adverse health consequences.

Travelers intending to visit a developing country should consult a travel medicine clinic or medical practitioner before the journey. This consultation should preferably take place 4 to 6 weeks before the journey, particularly if vaccination(s) may be required, but last-minute travelers can also benefit from a medical consultation, even as late as the day before travel. Such consultation can determine the need for vaccinations and/or prophylactic medication. 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 the visit, conditions of accommodation, and health status of the traveler. Medical advice and special precautions are also necessary for certain groups of high-risk travelers, including infants, pregnant women, the elderly, the disabled, 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.

Despite the risk of illness, the virtues of international travel are countless, and our intent as physicians should not be to burden the traveler with each and every potential infection or, worse yet, allude they would be better off avoiding travel. Our goal is to alert the traveler to potential hazards and be able to recognize CNS infection in the returning traveler.

How happy is the man who has traveled the ways

Of Jason or Ulysses, and then returned

To his home again, wise and having learned

To live among his own the rest of his day.

Joachim Du Bellay (1522–1560)

(Regrets, XXXI)

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TABLE 1
Potential Travel-Related Infections by Geographic Distribution*

Africa

North Africa

Dengue
Leishmaniasis
Malaria
Rift Valley fever
West Nile fever
Schistosomiasis
Brucellosis
Poliomyelitis (Egypt)

Central, East and West Africa

Malaria (falciparum)
Leishmaniasis
African sleeping sickness
Typhus
Plague
Viral hemorrhagic fever (eg Ebola, Marburg)
Yellow fever
Poliomyelitis
Meningococcal meningitis
Rabies

South Africa

Crimean-Congo hemorrhagic fever
Malaria
Plague
Relapsing fever
Rift Valley fever
Tick-bite fever
African sleeping sickness
Typhoid
Schistosomiasis

The Americas

North America

Lyme disease
Rocky Mountain spotted fever
Tularemia
Arthropod-borne encephalitis
West Nile virus

Mexico and Central America

Malaria
Leishmaniasis
Chagas disease

Dengue

Venezuelan equine encephalitis

Neurocysticercosis

Rabies

The Caribbean

Malaria (Haiti, Dominican Republic)

Dengue

Tularemia (Haiti)

Schistosomiasis

Rabies

Tropical South America

Malaria

Yellow fever

Epidemic viral encephalitis

Dengue

Schistosomiasis

Brucellosis

Arenavirus hemorrhagic fever

Rabies

Meningococcal meningitis

Temperate South America

Chagas disease

Malaria (NW Argentina)

Anthrax (mainland countries)

Rabies (Argentina, Chile)

Epidemic meningococcal meningitis (Chile)

Asia

East Asia

Malaria

Plague

Dengue

Japanese encephalitis

Schistosomiasis

Brucellosis

Leptospirosis

Rabies

Meningococcal meningitis

Southeast Asia

Malaria

Dengue

Japanese encephalitis

Plague

Typhoid

Rabies

Indian subcontinent, west central Asia

Malaria

Dengue

Japanese encephalitis

Crimean-Congo hemorrhagic fever

Poliomyelitis

Tick-borne hemorrhagic fevers

Middle East

West Nile virus (Israel)

Meningococcal meningitis (Mecca pilgrimage)

Crimean-Congo hemorrhagic fever

Typhoid

Schistosomiasis

Europe

Eastern and Western Europe

Tick-borne typhus

Tick-borne encephalitis

Lyme disease

West Nile virus

Rodent-borne hemorrhagic fevers

Oceania

Mosquito-borne viral encephalitis

Rabies (bat-bite)

Endemic malaria (Micronesia-Polynesia)

Epidemic dengue

* Adapted from *Health Information for International Travel 2001–2002* from the CDC.

TABLE 2
Practical Approach to an Ill Traveler

History

Travel history: date and places visited
Fever: duration, pattern
Potential exposures:
 Travel to rural areas
 Sexual exposure
 Freshwater swimming
 Ingestion of contaminated food
 Insect or animal bites
 Deep sea diving
Vaccination history
Use of prophylactic medication and compliance
Use of protective equipment
Immune status

Physical examination

Signs of meningism
Focal neurologic manifestations
Dermatologic manifestations
Involvement of other organ systems

Diagnosis

Basic blood work (CBC, BMP, LFT, urinalysis, blood culture)
Thick and thin blood film
Imaging studies (CT, MRI)
Lumbar puncture
Special tests (EEG)
Serology and viral identification

Management

Treat potential life-threatening complications
Assess for neurologic emergencies (status epilepticus, stroke, spinal cord compression)
Consider empiric broad-spectrum antibiotic, antiviral or antiparasitic coverage for very ill patients
Consult tropical or travel medicine expert

BMP indicates basic metabolic panel; CBC, complete blood picture; EEG; electroencephalogram; LFT, liver function test.

TABLE 3
Vectors of Infection and Prophylactic Measures

Vector	Potential Infection	Preventive Measure
Insects		
Mosquito	Malaria, arboviral encephalitides, VHF	Protective clothing, insect repellent, eradication of breeding places
Flea	Plague	Eradication of rodents
Tick	Tick-borne encephalitis, Congo-Crimean hemorrhagic fever	Personal protection
Fly	African trypanosomiasis, leishmaniasis	Personal protection, insect repellent
Animals		
Bites	Rabies	Pre- or postexposure prophylaxis
Excreta	Toxoplasmosis, leptospirosis	Avoid cat/rodent excreta
Ingestion		
Infected meat	Neurocysticercosis, vCJD, anthrax	Avoid uncooked/infected meat
Contaminated water	Polioomyelitis, cryptococcosis	Use safe water
Dairy products	Brucellosis, tuberculosis	Avoid unpasteurized dairy products
Poor sanitation	Enteric fever, amebiasis, cysticercosis, strongyloidiasis	Good personal hygiene and hand washing
Direct contact		
Sick contact	Meningococcal meningitis, viral infections, Lassa fever, Ebola, tuberculosis	Personal protection, control of body fluids, isolation of suspected cases
Sexual contact	HIV, syphilis, herpes	Safe sex, health education
Fresh water sports	Schistosomiasis, leptospirosis, acanthamoeba meningoencephalitis	Avoid freshwater exposure in endemic areas
Mud/dirt contact	Hook worm, leptospirosis, larva migrans	Wear shoes in endemic areas

TABLE 4

Treatment and Immunizations for Selected Infections

Infection	Chemoprophylaxis	Treatment	Vaccine	Note
Yellow fever	None	Supportive	Live vaccine	10 day before travel; provides life-long immunity
Japanese encephalitis	None	Supportive	Yes	Recommended for travel in Asia; angioedema occurs in 0.06% of vaccinees; protection lasts 3 years
Tick-borne encephalitis	None	Supportive	Inactivated whole virus	Recommended for travel in endemic areas of Europe; protection lasts 3 years
Poliomyelitis	None	Supportive	IPV	Recommended for travel in endemic areas; OPV not recommended
Rabies	None	Wound treatment, active and passive immunization	HDCV, PCEC, RIG	Preexposure for high-risk areas; protection lasts 2 years
Meningococcal meningitis	Not recommended, rifampin or ciprofloxacin if exposed	Cefotaxime, benzylpenicillin	Quadrivalent A, C, Y, W-135	Mandatory for travel to Saudi Arabia; child may require revaccination
<i>Haemophilus influenza</i>	Rifampin if exposed	Cefotaxime, benzylpenicillin	Hib vaccine	For infants, people 65 years of age or older, or splenectomized
Enteric fever	None	Ciprofloxacin, cefotaxime, chloramphenicol	Vi capsular parenteral or live-attenuated oral vaccine	Recommended for travelers to endemic areas; protection lasts 2 years
Malaria	Chloroquine, mefloquine, doxycycline, proguanil with chloroquine or atovaquone	Quinine, mefloquine, Fansidar, artemether, artesunate	None	Chemoprophylaxis recommended for travelers to endemic areas; consult travel medicine specialist to determine correct prophylaxis/treatment for area of travel

HDCV indicates human diploid cell vaccine; IPV, inactivated poliovirus; PCEC, purified chick embryo cell; RIG, rabies immunoglobulin.

TABLE 5
Resources

Web Resources

1. World Health Organization (WHO), <http://www.who.org>
2. Centers for Disease Control and Prevention (CDC), <http://www.cdc.gov/travel>
3. US Department of State, <http://www.travel.state.gov>
4. International Society of Travel Medicine, <http://www.istm.org>
5. Royal Society of Tropical Medicine and Hygiene, <http://www.rstmh.org>
6. American Society of Tropical Medicine and Hygiene, <http://www.astmh.org>
7. Travax Encompass, <http://www.travax.com>
8. Program for Monitoring Emerging Diseases (ProMED), <http://www.fas.org/promed>
9. *Emerging Infectious Diseases Journal (EIJ)*
10. *Mortality and Morbidity Weekly Report (MMWR)*

Books

The Yellow Book: Health Information for International Travel 2003–2004

The Blue Sheet: Summary of Health Information for International Travel

The Green Sheet: CDC's Inspection Scores of Cruise Ships

International Travel and Health: WHO, 2003

TABLE 6

Neurologic and Neuroimaging Findings and Treatment of Selected Parasitic CNS Infections

Parasite	Neurologic Effects	Neuroimaging Findings	Treatment
Chagas disease <i>Trypanosoma cruzi</i>	Headache, cognitive changes, seizures, tremor, hemiparesis	Large solitary or multiple ring-enhancing lesions with surrounding edema	Benznidazole 5 mg/kg/d in BID dosing for 60 days, or nifurtimox 10 mg/kg/d in TID or QID dosing for 120 days
Neurocysticercosis <i>Taenia solium</i>	Cognitive changes, meningismus, tremor, diplopia	Calcified, or enhancing lesions (homogenous or ring-enhancing), large cysts, may see scolex on MR imaging	Albendazole 15 mg/kg/d in BID dosing (max 400 mg BID) for 8–30 days, or praziquantel 50 mg/kg/d in TID dosing for 30 days
Schistosomiasis <i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Cauda equina or conus medullaris syndrome, transverse myelitis	Solitary or multiple hyperdense lesions in brain or spinal cord, may see "arborized" enhancement pattern	Praziquantel 60 mg/kg/d in 2 divided doses for 1 day or oxamniquine 15 mg/kg once
Paragonimiasis <i>Paragonimus westermani</i>	Headache, weakness, seizures, transverse myelitis, myelopathy	Clusters of ring-enhancing lesions	Praziquantel 75 mg/kg/d in 3 divided doses for 2 days; triclabendazole 10 mg/kg single oral dose or as 2 doses in 1 day; prolonged therapy may be required; steroids synergistic with Praziquantel
Echinococcosis <i>E. multilocularis</i> <i>E. granulosus</i>	Headache, seizures, signs of CNS mass effect	Cysts of various sizes, sometimes in grapelike clusters, granuloma	Albendazole 10–15 mg/kg/d in 2 divided doses for 3–6 months, or mebendazole 40–50 mg/kg/d in 3 divided doses for 3–6 months (maximum daily dose is 6 g); repeat treatments may be required, and cyst removal is usually necessary
Angiostrongylus <i>Angiostrongylus cantonensis</i>	Headache, hyperesthesia, cranial neuropathy, spinal cord impairment	Leptomeningeal enhancement and thickening, increased signal in basal ganglia, small hemorrhages	No effective treatment
Strongyloidiasis <i>Strongyloides stercoralis</i>	Headache, cognitive changes, meningismus, transverse myelitis, hemiparesis	Brain abscess or mycotic aneurysm	Ivermectin 200 µg/kg/d for 2 days every 2 weeks; bacterial meningitis due to enteric bacteria common during hyperinfection
Toxocariasis <i>Toxocara</i> spp.	Headache, fever, weakness, optic neuritis	Vasogenic edema with heterogenous enhancing lesion (s), subcortical and white matter disease resembling small-vessel vasculitis	Albendazole 400 mg BID or mebendazole 100–200 mg BID for 5 days

Compiled from references 91, 127–149.