

VIRAL HEPATITIS

Introduction

Hepatitis literally means inflammation of the liver. This section focuses on viral hepatitis, infection caused by a group of viruses that primarily affect the liver. Important forms of hepatitis to be discussed include hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV). Discussions address each of these infections because although they all cause “hepatitis,” their clinical pictures differ considerably.

Although other hepatitis viruses are gaining more prominence and are present in the Middle East, they are not discussed in detail here. The only one of these viruses that poses a potential threat is hepatitis E, a virus that clinically looks like HAV, causes an acute infection, and is spread by the fecal-oral route (Oldfield et al., 1991; Burans et al., 1994).

Epidemiologic Information

Hepatitis A is usually transmitted by the fecal-oral route. Infectious outbreaks occur where there is exposure to infected water or food (e.g., shellfish, commercial food preparation where an employee does not follow standard food handling guidelines) (Bean et al., 1996). Only in rare circumstances is this infection transmitted through parenteral routes. The Centers for Disease Control and Prevention estimates that between 125,000 and 200,000 infections occur annually in the United States, of which about 70 percent of adults are symptomatic. In rare circumstances (about 100 cases/year), HAV causes a lethal fulminant hepatitis. Serologic testing reveals that about one-third of Americans have evidence of past exposure to the virus. Periodic outbreaks occur. Groups at particularly high risk include household and sexual contacts of infected individuals, those who travel internationally, particularly to destinations where the

infection is endemic, American Indians, and people in close contact with infected patients, particularly during an outbreak. HAV is endemic in the Middle East, Africa, Asia, and Central and South America where the serologic prevalence of exposure to HAV has been reported to be as high as 96 percent (Oldfield et al., 1991; Heintges and Wand, 1997; el-Hazmi, 1989a).

Hepatitis B virus transmission occurs via parenteral routes with transmission through contact with infected blood, through sexual transmission, and from mother to child in the perinatal period. Risk groups include those who use intravenous drugs, individuals sexually active with multiple partners, homosexual men, infants born to infected mothers, hemodialysis patients, and healthcare workers. Hepatitis B is more common among lower socioeconomic groups; however, it is observed among all economic strata. The CDC estimates that there are between 140,000 and 320,000 infections annually in the United States with about half of them being symptomatic. Serologic evidence indicates a prevalence of between 1 and 1.25 million individuals with chronic Hepatitis B virus infection.

Hepatitis B is also common in areas where troops were deployed during Operation Desert Storm (Hyams et al., 1989; McCarthy et al., 1989). Serologic evidence suggests that the prevalence of Hepatitis B infection in Saudi Arabia is about 17 percent (Oldfield et al., 1991; el-Hazmi, 1989b). The incidence of HBV infection has decreased over the last decade as a result of the availability of vaccines and reduced high-risk behaviors.

Hepatitis C has been only recently recognized as a specific entity (Alter et al., 1998). The virus is responsible for the majority of cases of what was previously called non-A, non-B viral hepatitis. The CDC estimates that between 35,000 to 180,000 infections occur annually in the United States, of which up to 30 percent are symptomatic. Routes of transmission are similar to those for hepatitis B although risk factors differ. An estimated four million Americans are infected with HCV (Alter, 1997). This virus is also endemic in the Middle East (Al-Arabi et al., 1987; Bassily et al., 1983). Although the blood supply was previously responsible for a large number of transfusion-associated infections, the availability of commercially available screening tests has dramatically reduced this risk and improved the overall safety of the supply.

What Infected Patients Experience

The main clinical features of the three types of viral hepatitis are similar with the most common features being fatigue, abdominal discomfort, jaundice (yellowing of the skin and whites of the eyes), and loss of appetite.

Hepatitis A does not develop a chronic state although about 15 percent of patients experience a prolonged or relapsing course. Patients may have intermittent diarrhea and nausea. IgM anti-HAV antibody (indicating acute infection) appears approximately four weeks after exposure and rarely persists longer than six months.

Hepatitis B infections present with similar symptoms usually several weeks following infection. The findings are initially similar to those described for HAV, including a rare patient with fulminant disease who may die acutely from the infection. However, there are between 8,000 and 32,000 new chronic infections per year resulting in between 5,000 and 6,000 deaths annually from liver failure and liver cancer. Patients with chronic hepatitis are at risk for primary liver cancer (hepatocellular carcinoma) (Hoofnagle and di Bisceglie, 1997).

Hepatitis C has a similar presentation to the other viruses; however, the risk of chronic infection is much higher with this virus (at least 85 to 90 percent). Consequently, chronic liver disease develops in the majority of patients and the risk of death from chronic liver disease is much higher in these patients (about 8,000 to 10,000 deaths per year) (Hoofnagle, 1997).

Diagnosis

Diagnosis of the common hepatitis infections is easily made through laboratory tests. In fact, the availability of these techniques has dramatically reduced the risk of transfusion-transmitted disease because these tests are commonly used to screen all blood donors. There are tests that will diagnose current, chronic, and past hepatitis infections, depending on the patient's condition and the virus involved.

Treatment and Prevention

Treatment for HAV is primarily supportive because of its self-limited nature (Koff, 1998; Lemon, 1997). Treating HBV and HCV infections is also supportive; however, because of the risk of chronic liver disease, including hepatocellular carcinoma and cirrhosis, interferon and other medications are available to retard the development of the long-term complications of chronic disease. For patients who develop end-stage liver disease, surgical interventions can reduce the morbidity of disease. Liver transplant remains an option for those patients who are refractory to other treatments and who develop life-threatening liver failure. Newer treatments and complementary therapies continue to be developed (Bonkovsky, 1997; Brady 1997; Damen et al., 1998; Everhart et al., 1997; Inchauspe, 1997).

Prevention of those hepatitis infections transmitted by the fecal-oral route involves standard hygiene and sanitation techniques. It is important for food handlers to adhere to proper food preparation standards. Immunoglobulin can be given to individuals prophylactically or patients with known recent exposure can receive anti-HA immunoglobulin. Recently, a hepatitis A vaccine became available that reduces the risk of HAV disease. Immune globulin is also available to the nonimmune patient who is exposed. Vaccines for HBV have been available since 1982 and have been instrumental in reducing the risk of infection from this virus (Zannolli and Morgese, 1997; Zimmerman et al., 1997). Infants and children are now routinely vaccinated, and recommendations exist to vaccinate others in high-risk groups (e.g., healthcare workers, homosexual men). Blood and tissue donor screening also reduces the risk of transmission to recipients. Community programs can reduce transmission through recreational intravenous drugs. For HCV, screening of blood and tissue donors and reduction of risky behaviors can help reduce the transmission rate. A vaccination to prevent transmission of HCV is not yet available.

Correlation with Gulf War Illnesses

Although all the forms of hepatitis discussed in this review exist in the Middle East, the primary concern during the deployment centered on those infections that are transmitted via the fecal-oral route. Particularly because the risk of transmission is increased when individuals live in close proximity, this was a concern during Operation Desert Storm. However, because many patients infected with the hepatitis viruses are symptomatic, the absence of specific symptoms (e.g., jaundice) and the absence of an increased prevalence of laboratory tests positive for infection suggest that hepatitis is not responsible for the symptoms experienced by individuals with undiagnosed Gulf War illnesses. Immune gamma-globulin was used in service members to prevent hepatitis A infection (Lashof et al., 1996). However, given the high prevalence of these diseases, it is not surprising that some veterans, like civilians, will be infected with hepatitis viruses through other routes of exposure.

Summary

The group of hepatitis viruses primarily infect the liver with resultant gastrointestinal and systemic manifestations. These infections are common in the Middle East and in the United States. Although it is expected that some veterans will have hepatitis, the presence of the infection does not imply that military service is the etiology of the exposure.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Introduction

Crimean-Congo hemorrhagic fever is caused by a virus that is part of the Bunyaviridae family, genus Nairovirus. This infection is emerging as an important zoonotic disease (animal disease transmitted to humans). The virus has been identified throughout sub-Saharan Africa, the Middle East, Asia, and Eastern Europe.

The disease is transmitted from the bite of the *Hyalomma* tick, although nosocomial and household transmission to humans has been observed. Cattle, sheep, and wild hares appear to be the most important animal reservoirs for the virus although *Hyalomma* are attracted to humans.

Epidemiologic Information

The virus has been identified in outbreaks in the Soviet Union, Bulgaria, Pakistan, Iraq, Dubai, Kuwait, and the United Arab Emirates (Gubler and Clark, 1995; Kwiatkowski and Marsh, 1997; Kitua, 1997; Soares and Rodrigues, 1998; Connor et al., 1998; Greenwood, 1997; Facer and Tanner, 1997; Dubois and Pereira da Silva, 1995). The disease is fairly common among some populations in Iraq. Tikriti and colleagues observed that nearly 30 percent of animal breeders tested had antibodies to the virus (Tikriti et al., 1981).

Although a less common route of infection, as indicated, nosocomial infection has been observed in most of the geographic areas in which the virus is endemic. When infection has occurred, there have been high fatality rates. This means that strict blood and body fluid precautions must be taken when infection is even suspected.

What Infected Patients Experience

The incubation period for the virus ranges from three to 12 days, followed by sudden onset of severe headaches. Fever, accompanied by shaking chills, is also present initially or shortly thereafter. The fever usually lasts for about a week or slightly longer with about half of those affected experiencing a 12- to 48-hour afebrile period sometime in the middle of the illness (i.e., a double peaked fever curve) (Oldfield et al., 1991).

The fever is frequently accompanied by muscle aches (particularly in the low back and legs), sore throat, and photophobia. Many patients have accompanying nausea and vomiting. Gastrointestinal complaints, in half of infected patients, include diffuse abdominal pain and diarrhea. Patients may also develop

hepatomegaly (enlarged liver) and right upper quadrant abdominal pain. Facial flushing, possibly involving the upper torso, also occurs. Bradycardia is also observed.

After several days, a petechial rash develops that is associated with epistaxis, hematemesis, and melena (Oldfield et al., 1991), which are manifestations of the ensuing disseminated intravascular coagulation (DIC). The fatality rate for this virus is between 13 and 70 percent, occurring between days six and 14 of the illness (Oldfield et al., 1991; Schwarz et al., 1997).

Diagnosis

Laboratory tests and serologic assays are available that specifically identify the virus and detect host response to the virus (Burt et al., 1994). More recently, a polymerase chain reaction molecular diagnostic protocol has emerged (Burt et al., 1998).

Treatment and Prevention

The treatment for infected patients is primarily supportive. However, recent efforts have shown promising results for specific therapies, including ribavirin and specific intravenous immunoglobulin (Centers for Disease Control and Prevention, 1995; Fisher-Hoch et al., 1995; Tignor and Hanham, 1993; Vassilenko et al., 1990).

Prevention involves reducing exposure to the ticks in endemic areas through the use of pesticides (e.g., DEET) and protective clothing. Individuals should look for and remove ticks on their bodies. In the clinical setting, including the clinical laboratory, methods must be taken to avoid contact with blood and body fluids of potentially infected patients.

Correlation with Gulf War Illnesses

There were no identified cases of Crimean-Congo hemorrhagic fever among individuals who served in the Gulf War (Richards et al., 1991). Because this disease is profoundly symptomatic in infected individuals and diagnostic tests are available to identify infection, Crimean-Congo hemorrhagic fever is unlikely to be the cause of the chronic illnesses experienced by some Gulf War veterans.

Summary

Crimean-Congo hemorrhagic fever is a viral infection that is well known in the areas where U.S. troops served in the Gulf War. The infection is passed to

humans from the bite of the *Hyalomma* tick, but nosocomial and household transmission have also been observed. No individuals studied show evidence of contracting Crimean-Congo hemorrhagic fever and the clinical presentation is inconsistent with what is observed in patients with undiagnosed Gulf War illnesses.

WEST NILE FEVER

Introduction

West Nile fever is caused by a virus that is part of the Flaviviridae family. There are nearly 70 different viruses in this group, formerly termed group B arboviruses, of which nearly half are known to cause illness in humans. The World Health Organization defines arboviruses (arthropod-borne viruses) as a group as those “which are maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by hematophagous arthropods; they multiply and produce viremia in the vertebrates, multiply in the tissues of arthropods, and are passed on to new vertebrates by the bites of arthropods after a period of extrinsic incubation” (Sanford, 1991). Common viruses in this classification, in addition to West Nile, include yellow fever, dengue, Japanese encephalitis, St. Louis encephalitis, and tick-borne encephalitis viruses. These viruses are generally spread by mosquitoes or ticks; human-to-human spread does not occur. Infection with these viruses does not produce a unique clinical picture. Therefore, travel to an endemic area and laboratory tests are important for identifying a specific infection.

West Nile virus is a mosquito-borne virus found most commonly in Africa, France, India, Indonesia, the Middle East, and Soviet countries. In 1999, a West-Nile-like virus was identified in patients living in the Northeast United States. The bird is the primary host and the principal vector is *Culex univittatus*. However, other mosquitoes are known to carry the virus, including *Culex pipiens*, *Culex antennatus*, and *Culex tritaeniorhynchus* (Asia). Other animal reservoirs are not part of the virus’s normal life cycle.

Epidemiologic Information

West Nile fever is common in the Middle East with most individuals exposed as children. Children experience a nondescript viral illness with fever that is rarely diagnosed. Neighboring Israel also experiences infection although there, it is more likely the young adult than the child who becomes infected. Spread occurs primarily in the summer months when the mosquito population increases.

What Infected Patients Experience

The incubation period for the virus is between one and six days. After the incubation period, the patient's temperature rises rapidly to between 101°F and 104°F accompanied with nonspecific symptoms associated with fever, including drowsiness, a severe frontal headache, ocular pain, and abdominal and back pain. In addition, patients experience facial flushing, conjunctival injection (red eyes), and coating of the tongue, accompanied by moderate lymph node enlargement (occipital, axillary, inguinal) with some tenderness (Sanford, 1991). About one third of patients experience chills. Half of infected patients experience a rash between one and four days after onset of the illness that lasts from a few hours to until the fever breaks. In most patients, the illness is self-limited, resolving over a few days with lymph node enlargement decreasing over a few months. Rarely are long-term complications observed, and fatalities are extremely rare.

Diagnosis

Nonspecific laboratory tests include leukopenia (total white blood cell count less than 4000/ μ L). Definitive diagnostic tests exist, in the form of viral isolation (during infection) or the identification of a rising specific antibody titer.

Treatment and Prevention

For infected patients, the goal is to treat the symptoms. There are no specific treatments for West Nile fever. Prevention involves reducing exposure to the mosquito population in endemic areas.

Correlation with Gulf War Illnesses

There was one confirmed case of West Nile fever among individuals serving in the Gulf War (Hyams et al., 1995; Richards et al., 1991). Furthermore, the insect vector was identified in the area (Cope et al., 1996). However, the use of insecticides and troop deployment in the cooler months led to conditions that were not favorable to the transmission of this virus. Because this disease is self-limited and diagnostic tests are available to identify infection, West Nile fever is unlikely to be the cause of the chronic illnesses experienced by some Gulf War veterans.

Summary

West Nile fever is a viral infection common in Africa, the Middle East, some areas within Europe, India, Indonesia, and in Soviet countries. It is normally

passed from mosquito to bird and back to mosquito. Human involvement in this cycle is incidental. West Nile fever is a self-limited febrile illness; few patients experience any long-term sequelae from the infection. Infection is easily diagnosed through common laboratory tests. Although one individual serving in the Gulf War did contract West Nile fever, the clinical presentation is inconsistent with what is observed in patients with undiagnosed Gulf War illnesses.

SINDBIS

Introduction

Sindbis is a vector-borne alphavirus that produces a disease characterized by fever, rash, and polyarthritides. This virus, native to Africa, Scandinavia, former Soviet countries, Australia, and Asia (Norder et al., 1996), is part of the *Togaviridae* family, which includes the more commonly recognized eastern equine encephalitis and western equine encephalitis viruses. The most recognized member of the *Togaviridae* family is the virus that causes rubella. The virus is a positive-stranded RNA virus.

Epidemiologic Information

Sindbis was first described in 1961, during an outbreak of five cases in Uganda (Niklasson, 1998). The Sindbis virus exists among birds, transmitted primarily by *Culex* mosquitoes. A South African study demonstrated the clear association between human disease outbreaks and excessive rainfall, particularly when water stands in usually dry areas. Infection rates may approach 15 percent of the susceptible population in particularly favorable settings. Sindbis shares its vector with that of the West Nile virus. The pattern of this vector is discussed in greater detail in the West Nile virus section above. Because of this common viral vector, in the Middle East it is common to find individuals who are positive for exposure to Sindbis to also be positive for exposure to West Nile virus.

What Infected Patients Experience

Sindbis usually presents as a sudden onset of low-grade fever after an incubation period of usually less than one week (Niklasson, 1998). Patients experience accompanying myalgias, malaise, and arthralgia that affect the joints and tendons. The joints involved include the wrist (50 percent), fingers (18 percent), hips (26 percent), knee (42 percent), and ankle (62 percent). Swollen joints do not show significant fluid accumulation. The key feature of Sindbis is the maculopapular nonpruritic (6 percent of patients report itchiness) rash on the trunk and extremities that becomes vesicular, particularly on the extremities. The papules are approximately 3 mm in diameter. The rash is present for an aver-

age of one week (range 1 to 21 days). Although the rash and fever are almost always gone after three weeks, arthralgia may persist for many months in some cases (Niklasson, 1988). Fatal cases of Sindbis have not been reported.

Diagnosis

The virus can be isolated from blood or vesicle fluid during the acute phase of the infection. Nonspecific laboratory tests include mild leukopenia and elevation of acute phase reactants. In addition to these nonspecific findings, definitive diagnostic tests exist, particularly the identification of a rising specific antibody titer.

Treatment and Prevention

As with other members of this virus group, treatment is supportive and with time (usually a short period but perhaps up to several months), the symptoms resolve. Prevention, as with other arboviruses, centers on decreased exposure to the potentially infective mosquito through the use of repellants and the wearing of clothing that covers the body, particularly when the mosquito population is abundant (Peters and Dalrymple, 1990).

Correlation with Gulf War Illnesses

There were no identified cases of Sindbis among individuals who served in the Gulf War (Richards et al., 1991). The presentation and course of this disease is not consistent with the findings of those individuals with undiagnosed illnesses associated with Gulf War service, even though some of the initial findings may bear a similarity to Gulf War veterans' symptoms. Sindbis, therefore, is unlikely to be the cause of the chronic illnesses experienced by Gulf War veterans.

Summary

Sindbis is an arbovirus that produces fever, rash, and polyarthrititis. The virus is transmitted to humans through *Culex* mosquitoes. No cases of sindbis have been identified among individuals serving in the Gulf War and the chronic symptoms among Gulf War veterans with undiagnosed illnesses are not generally characteristic of this infection.

RIFT VALLEY FEVER

Introduction

Rift Valley fever is an acute, fever-causing viral disease that affects domestic animals (e.g., cattle, buffalo, sheep, goats, and camels) and humans. Rift Valley fever is most commonly associated with mosquito-borne epidemics during years of heavy rainfall.¹ Rift Valley fever virus is a Phlebovirus in the family Bunyaviridae. Other viruses within this family include California encephalitis virus, Crimean-Congo hemorrhagic fever, and hantavirus.

People get Rift Valley fever from the bites of mosquitoes (*Aedes mcintoshi*, *Culex pipiens*, *Eretmapodites chrysogaster*, *Aedes caballus*, *Aedes circumluteolus*, *Culex theileri*) and possibly other blood-sucking insects that serve as vectors. People can also get the disease if they are exposed to either the blood or other body fluids of infected animals. Therefore, increased risk of infection is seen in farmers, veterinarians, and others who handle infected animals and carcasses. Individuals handling laboratory specimens have also become infected, suggesting an aerosol transmission route.

Epidemiologic Information

Rift Valley fever occurs in regions of eastern and southern Africa where sheep and cattle are raised, although the infection is also seen in most countries of sub-Saharan Africa and Madagascar. The virus primarily affects livestock and can cause disease in a large number of domestic animals. The presence of a Rift Valley fever epizootic can lead to an epidemic in people exposed to diseased animals.

Infection is transmitted from generation to generation of mosquitoes through the eggs of infected mosquitoes. It is possible for infected eggs to remain dormant in soil for extended periods of time, only to emerge when moisture returns, as in the case of heavy rains or man-made events that alter environmental moisture.

What Infected Patients Experience

Most patients experience a nonspecific febrile reaction. After an incubation period of three to six days, the patient's temperature rises rapidly to 101°F to 104°F. Initial onset of fever may be accompanied by chills, malaise, headache, retroorbital pain, and backache. Some patients may experience nausea and

¹CDC website: <http://www.cdc.gov/ncidod/dvrd/rvf/rvf.htm>.

vomiting (Arthur et al., 1993). Later, patients may experience anorexia, epigastric pain, and photophobia. Patients may experience defervescence after two to three days, followed by a second temperature spike before resolution. For most patients, Rift Valley fever is considered a benign, self-limited disease.

Between 1 and 5 percent of individuals develop ocular problems, including retinitis and vasculitis that results in some degree of permanent visual loss among about half the affected patients. Rarely (in about 1 percent), at the end of the febrile period, patients develop severe fulminant disease that can include encephalitis, hemorrhage, jaundice, and hepatitis. When such serious manifestations occur, 50 percent or more may die.

Diagnosis

Rift Valley fever can be diagnosed easily through laboratory testing. During the infectious period, the virus can be isolated from blood (in about 75 percent of patients) and by detection of antibodies that are present four to 14 days after onset of disease, coinciding with clinical improvement.

Treatment and Prevention

Treatment of patients is symptomatic; there are no specific treatments for Rift Valley fever. Prevention involves avoidance of mosquitoes when traveling to endemic areas and reducing exposure to potentially infected animal products and laboratory specimens.

Correlation with Gulf War Illnesses

There were no identified cases of Rift Valley fever among individuals who served in the Gulf War (Richards et al., 1991). The insect vector was identified in the area (Cope et al., 1996). However, the use of insecticides and troop deployment in the cooler months led to conditions that were not favorable to the transmission of this virus. Because this disease is self-limited and diagnostic tests are available to identify infection, Rift Valley fever is unlikely to be the cause of the chronic illnesses experienced by some Gulf War veterans.

Summary

Rift Valley fever is a viral infection common in areas in and around the Persian Gulf and Africa. There was concern that U.S. service members may have been exposed. The virus is normally passed from mosquito to animals, particularly sheep and cattle, and back to mosquito. Human infection occurs through

mosquito bites, from handling infected animal tissues, and from failure to take adequate precautions when handling infectious laboratory specimens. Rift Valley fever is generally a self-limited febrile illness, although a small percentage of individuals experience a fulminant infection with high mortality. Infection is easily diagnosed through common laboratory tests. No individuals studied show evidence of contracting Rift Valley fever (Hyams et al., 1995) and the clinical presentation is inconsistent with what is observed in patients with undiagnosed Gulf War illnesses.

RABIES

Introduction

Rabies is caused by a number of different viruses within the Rhabdoviridae family and was first recognized more than 4,000 years ago. Although the virus has been classically associated with dogs and dog bites, rabies can affect a large number of wild and domesticated animal species. Because the virus exists in the Gulf region, some individuals raised the question whether rabies might contribute to the illness experienced among Gulf War veterans.

Epidemiologic Information

Rabies has been reported on all continents except Australia and Antarctica. Over the last half century, there has been a dramatic decrease in rabies among domestic animals in the United States. This has been accompanied by the consequent decrease in human cases to fewer than two cases per year in the 1960s and 1970s and fewer than one case per year during the 1980s (Reid-Sanden et al., 1990). Therefore, the likelihood of exposure to a rabid domestic animal is very low, although many possible exposures occur that constitute the basis for antirabies treatment (Helmick, 1983).

Only about 1,000 rabies deaths are reported to the World Health Organization annually, even though the annual incidence of rabies is believed to be about 30,000 cases. The disease is most common in Southeast Asia, the Philippines, Africa, the Indian subcontinent, and tropical areas of South America (Corey, 1991).

Rabies among wild animals (especially skunks, raccoons, and bats) has accounted for more than 85 percent of all reported cases of animal rabies every year since 1976 in the United States (Gonzalez-Ruiz et al., 1994). Wild animals are now the most important potential source of infection for both humans and domestic animals in the United States. However, in much of the rest of the world, including most of Asia, Africa, and Latin America, the dog remains the

major species with rabies and the major source of rabies among humans (Centers for Disease Control and Prevention, 1991).

Rabies is transmitted to humans only when the virus is introduced through open cuts or wounds in skin or mucous membranes via bites or infected animal saliva. The likelihood of contracting rabies varies with the type of exposures.

What Infected Patients Experience

After the incubation period of weeks to many months, the disease initially presents with a nonspecific prodromal phase in from 50 to 80 percent of patients. This period lasts from one to 10 days. Patients experience severe fever, headache, malaise, myalgias, easy fatigability, and cough. Early neurologic involvement may precipitate apprehension, anxiety, agitation, irritability, nervousness, insomnia, psychiatric abnormalities, or depression (Fishbein and Bernard, 1995).

Following the conclusion of the prodromal phase, the patient progresses to the encephalitic or acute neurologic phase. At this stage, which lasts usually from two to seven days, neurologic manifestations are extreme. Almost all patients die from one or more systemic complication of rabies.

Diagnosis

At first, the laboratory findings are generally either normal or nonspecific. The specific diagnosis requires either isolation of the virus from infected body fluids or the demonstration of serologic evidence for infection. Clinically, it is difficult to distinguish rabies from other viral infections that produce similar findings (Corey, 1991; Fishbein and Bernard, 1995).

Treatment and Prevention

Because rabies is virtually 100 percent fatal without intervention, prevention is critical. The most important means of prevention is the control of the virus in animal populations, particularly domestic animals. Pre- and postexposure prophylaxis is also important in preventing the devastating consequences of this disease.

Correlation with Gulf War Illnesses

The clinical findings, as discussed above, are not consistent with the findings of individuals who have undiagnosed Gulf War illnesses. Although some of the early signs and symptoms of rabies may have some resemblance to Gulf War

illnesses, the 100 percent case-fatality rate is entirely inconsistent with chronic symptoms.

Summary

Rabies is a serious infection, transmitted to humans through the bite of infected animals. This infection has a very high case-fatality rate. Although endemic in most parts of the world, including areas where U.S. military visited during the Gulf War, rabies cannot be the etiology for unexplained Gulf War illnesses. There are good diagnostic tests for rabies. That, combined with the clinical outcome of the disease, excludes this infection from the list of possible causes for unexplained symptoms in Gulf War veterans.

DENGUE

Introduction

Dengue fever is caused by a virus that is part of the Flaviviridae family. There are nearly 70 different viruses in this group, formerly termed group B arboviruses, of which nearly half are known to cause illness in humans. Other common viruses in this classification include yellow fever, West Nile, Japanese encephalitis, St. Louis encephalitis, and tick-borne encephalitis viruses. The most common infection in humans is caused by the dengue virus, of which there are four types. Flaviviruses are generally spread by mosquitoes or ticks; human-to-human spread does not occur. Infection with these viruses does not produce a unique clinical picture. Therefore, travel to an endemic area and laboratory tests are important for identifying specific infection.

Dengue and dengue hemorrhagic fever (DHF) are caused by infection with one of four antigenically distinct, virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Once infected with one of these serotypes, the individual develops specific immunity. However, cross-immunity does not develop. It is theoretically possible, therefore, for an individual to be infected four times, each time with a different serotype.

Dengue is mostly seen in tropical urban areas. As with other members of the Flaviviridae family, the virus is transmitted through mosquito bites, specifically *Aedes aegypti*. This mosquito, a domestic, day-biting mosquito, prefers to feed on humans (Gubler and Clark, 1995). In some parts of the world (mostly Asia and Oceania) other vectors have been implicated: *A. albopictus*, *A. scutellaris*, and *A. polynesiensis*.

Epidemiologic Information

Dengue is the most important mosquito-borne viral disease, affecting humans with a distribution comparable to that of malaria. Approximately 2.5 billion people are living in areas at risk for epidemic transmission (Gubler and Clark, 1995). Tens of millions of cases of dengue fever occur annually along with up to hundreds of thousands of cases of dengue hemorrhagic fever.

What Infected Patients Experience

Dengue infection can produce a broad range of clinical findings. Common findings, described during an outbreak in U.S. troops during Operation Restore Hope in Somalia during 1992–1993 include fever (mean temperature on admission in this group was 102°F) (100 percent), chills (93 percent), myalgias (84 percent), headache (86 percent), retro-orbital pain (53 percent), rash (49 percent), pharyngitis (30 percent), cough (28 percent), and conjunctivitis (17 percent) (Sharp et al., 1995). The incubation period ranges from two to seven days, after which fever appears rapidly, along with the other findings noted above. Joint and bone pain are also prevalent. There is generally a rash during the first few days of illness, followed by anorexia, nausea, vomiting and frequently respiratory manifestations that mimic a cold or flu. The fever usually breaks after three to six days, followed by a maculopapular or morbilliform rash on the trunk, spreading to the limbs and face and resolving after a few days. Patients then recover over several weeks although the convalescent period may extend a few more weeks. Dengue does not cause persistent or recurrent musculoskeletal complaints or arthritis (Monath, 1995).

Dengue hemorrhagic fever is the most serious manifestation of the disease. This process, an immunologic reaction, occurs for the most part in individuals already sensitized to the disease, either actively through infection or passively in infants through placental transfer of immunoglobulin from mother to child.

Initially, dengue hemorrhagic fever appears the same as dengue but after several days the patient deteriorates with prostration, restlessness, signs of circulatory collapse (diaphoresis, cold extremities, dyspnea, circumoral and peripheral cyanosis, and hemorrhagic manifestations). Available laboratory tests cannot identify who will ultimately develop this manifestation.

Diagnosis

Because the clinical presentation of dengue is not distinguishable from other infectious diseases, the diagnosis is made by laboratory testing. Laboratory tests available include isolation of the virus, demonstrating the presence of the

viral antigen using immunoassay tests, or amplification of the viral nucleic acids using the polymerase chain reaction process (Sudiro et al., 1997). Patient sera can be used to test for the presence of anti-dengue virus antibody; demonstrating a significant increase in the antibody titer between the acute and convalescent sera confirms the infection. This has been an effective way to study exposure of U.S. troops deployed to areas where dengue is endemic (Sharp et al., 1995).

Treatment and Prevention

Dengue is treated by managing the patient's symptoms, rather than a specific treatment such as an antiviral agent. Patients suspected of infection should ensure that they are safe from additional mosquito bites.

No vaccines currently available protect against dengue, although several are undergoing investigation. The Centers for Disease Control and Prevention predicts that an effective vaccine will be available within the next decade.

Correlation with Gulf War Illnesses

Although some of the clinical findings of individuals with Gulf War illnesses have some minor similarities to the presenting findings of dengue, this infection does not cause chronic disease. Furthermore, laboratory testing is available to detect infection with dengue virus. No evidence of incident cases of dengue fever was found among those who served in the Gulf War (Richards et al., 1991).

Summary

Dengue and dengue hemorrhagic fever represent an important infection in tropical areas. The virus is spread through mosquitoes, manifests itself by non-specific findings, and has no specific treatment once the cause is identified. A chronic state of this viral infection is not known, and laboratory tests are readily available to detect infection. Increased antibody titers have not been observed in individuals who served in the Gulf War. Therefore, dengue is not a likely cause for unexplained chronic symptoms among Gulf War veterans.

SANDFLY FEVER

Introduction

Sandfly fever is also known as Phlebotomus fever, pappataci fever, and three-day fever. The disease is caused by the phleboviruses that are part of the Bun-

yaviridae family. There are at least five different phleboviruses, distinguished by their immunologic characteristics. Of these five types, two (Sicilian virus and Naples virus) are endemic in the Middle East. Infection with the virus causes a self-limited febrile illness.

During World War II, sandfly fever was a major problem for U.S. forces, with 19,000 cases reported (Oldfield et al., 1991). The highest incidence was in the Middle East, so military leaders were aware of the risk of sandfly fever during the Persian Gulf deployment. During World War II, attack rates were 3 to 10 percent of all troops, but among some units, the attack rate exceeded 50 percent. From a military standpoint, sandfly fever is a serious threat, since a large number of individuals can become infected and ill within a short period of time.

Epidemiologic Information

Sandfly fever is known to occur throughout the Middle East, the Mediterranean area, the Balkans, eastern Africa, and other neighboring areas. Most natives acquire the infection early in life and remain immune. The vector for this infection is the sandfly, *Phlebotomus papatasi*. Sandflies are small urban flies that are about 2 to 3 mm in size. Most patients (99 percent) who are bitten by the sandfly are unaware that they were bitten. The sandfly is the same vector responsible for transmitting *Leishmania* (Tesh, 1989).

The sandfly is primarily a nocturnal insect with the largest numbers appearing from April to October. (See the vector plots in Figure 6.1.) The female fly transmits the disease, starting about a week after she acquires the infection from an infected human host. The fly remains infected throughout life (about four more weeks). The gerbil may be a possible reservoir; however, the infected human is generally considered to be the primary host and source of infection for the sandfly.

What Infected Patients Experience

As one of its names implies, the illness associated with sandfly fever is of a short duration, generally on the order of two to four days. The incubation period is from three to six days, followed by a sudden onset of symptoms. Fever is usually the first, peaking sometimes as high as 105°F. Patients may experience severe frontal headaches, retroorbital pain, photophobia, arthralgias, and muscle aches. Nausea, vomiting, abdominal pain, and diarrhea may also occur. Some patients also have symptoms during infection that suggest an aseptic meningitis, at times sufficient to warrant evaluation of spinal fluid (Schwarz et al., 1995). After the initial three days, the fever gradually decreases. During convalescence, patients can experience giddiness, weakness, and depression

(Sanford, 1991). About 15 percent of patients experience a second attack between 2 and 12 weeks after the initial infection. Because of past experience, outcomes from this disease are well studied. Mortality is not observed.

Diagnosis

The infection can be made based on isolation of the virus starting just before fever onset and continuing for a day after onset. Serologic tests are also available for diagnosis of the infection.

Treatment and Prevention

Treatment is generally supportive in nature. Although some advocate ribavirin as a potential treatment, supportive care usually results in resolution of symptoms in a relatively short period of time.

Prevention centers on avoidance of sandfly bites. Spread can be prevented by using insecticides and mosquito nets to protect the infected individual from sustaining another bite, permitting subsequent transmission to an uninfected host. Further information can be found in the review of *Leishmania* by Oldfield and colleagues (1991).

Correlation with Gulf War Illnesses

No cases of sandfly fever were reported among Gulf War veterans, in contrast to the 30 cases of sandfly fever per 1,000 population (among those deployed to the Middle East) during World War II in the Persian Gulf region. The time of year when most troops were deployed during the Gulf War favored the low rate of *Leishmania* infection and the absence of sandfly fever. The prevalence of *P. papatasi* depends on environmental conditions; the sandfly is sensitive to temperature extremes and low humidity. Cross and colleagues (1996) used weather station and satellite data to model Persian Gulf weather conditions and predict the seasonal distribution of the sandfly. As diagrammed in Figure 6.1, the highest sandfly prevalence, and thus the highest risk of both *Leishmania* and sandfly fever, occurs in the spring and summer months. Laboratory studies among Gulf War veterans have failed to demonstrate any evidence of exposure to, or infection by, the sandfly fever virus (Richards et al., 1991).

Summary

Sandfly fever was a significant source of morbidity in previous military engagements. Protective measures, including mosquito nets and insecticides along

with the timing of the operation, may have contributed to the lack of incident cases. A chronic state of this viral infection is not known, and laboratory tests are readily available to detect infection. Increased antibody titers have not been observed in individuals who served in the Gulf War. These combined findings suggest that sandfly fever is not a cause of the symptoms experienced by some individuals with Gulf War illnesses.

LEISHMANIAVIRUS

Introduction

Leishmanivirus is a relatively recently recognized double-stranded RNA virus that infects some strains of *Leishmania*. This virus is a member of the family Totiviridae, a group of viruses that infect protozoa and fungi (Saiz et al., 1998). Viruses that infect protozoan parasites were first recognized in the 1960s; however, *Leishmania*-infecting viruses were discovered in 1988 (Chung et al., 1994). Although the molecular characteristics of this group of viruses have recently been elucidated, its relationship to clinical disease is essentially unknown. Leishmanivirus has some unusual characteristics; specifically, a viral capsid protein is an RNA endonuclease that may be responsible for some of the viral persistence characteristics (MacBeth and Patterson, 1995). The virus has been detected in cultured *L. braziliensis*, *L. guyanensis*, and *L. major* (Saiz et al., 1998).

Epidemiologic Information

Little is known about this virus. However, in a study of human biopsy tissues collected in 1996 as part of a drug treatment program in Cuzco, Peru, viral RNA was identified in two of 11 samples studied by molecular diagnostic techniques (Saiz et al., 1998).

What Infected Patients Experience

Much more evaluation needs to be completed to understand whether infection of *Leishmania* with Leishmanivirus alters the pathogenesis of the protozoa in humans. What clinical manifestations, if any, result from this infection would be speculative.

Diagnosis

The diagnosis of infection with Leishmanivirus in patients who harbor a *Leishmania* infection is made through the use of molecular diagnostic tech-

niques (Saiz et al., 1998). However, this diagnostic technique is currently performed only in specialized research laboratories.

Treatment and Prevention

Because this virus is present only in patients infected by *Leishmania*, the treatment and prevention are the same as those described in the discussion on *Leishmania*.

Correlation with Gulf War Illnesses

Because so little is known about this infection, correlation with unexplained Gulf War illnesses cannot be made at this time. However, because of the low rate of *Leishmania* among those who served in the Gulf War, it is unlikely that many, if any, veterans harbor this virus.

Summary

Leishmanivirus is a newly described double-stranded RNA virus that has been found in some cases of *Leishmania* infections in Peru. Further research is needed to sufficiently understand the role of this virus in the pathogenesis of human disease. There is some speculation that the virus might modify the protozoan infection and influence the manifestations of disease in patients infected with *Leishmania*. At present, however, there is no evidence that a sufficient number of patients are infected with *Leishmania* that Leishmanivirus could be present in more than, at most, a few individuals who served in the Gulf War.