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TROPICAL INFECTIOUS DISEASES

Principles, Pathogens and Practice

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CHAPTER 72

Sandfly Fever, Oropouche Fever, and Other Bunyavirus Infections

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INTRODUCTION

The family *Bunyaviridae* includes more than 300 antigenically distinct members, most of which are transmitted by arthropods.[1] At least 41 of these viruses have been associated with human illness in the tropics. Apart from those members that produce serious and sometimes fatal disease (i.e., the hantaviruses, Rift Valley fever virus, and Crimean-Congo hemorrhagic fever virus), most of the remaining human pathogenic bunyaviruses produce nonspecific febrile illnesses. Because of their nonspecific nature and the limited virus diagnostic capabilities in many tropical countries, these infections are often unrecognized or are misdiagnosed as other common febrile illnesses such as malaria or dengue. This chapter describes some of the more common bunyavirus fevers.

PHLEBOTOMUS (SANDFLY) FEVER

Historically, phlebotomus fever (PF) has been mainly a disease of military importance, since epidemics have typically occurred when large numbers of nonimmune adults enter an area of endemic virus activity. The disease occurred in troops during the Napoleonic Wars, the Austrian occupation of the Adriatic, the British colonization of India and Pakistan, and the North African and Mediterranean campaigns in World War II.[2,3] The largest reported outbreak of PF occurred in Serbia in 1948, when over 1 million persons were affected. PF outbreaks still occur among tourists vacationing in the Mediterranean region.[4–7]

Many of the PF group of viruses appear to be maintained in their insect vectors by vertical (transovarial) virus transmission.[3] Consequently, virus activity is largely correlated with adult sandfly activity rather than by the immune status of the local human or animal populations. During periods of vector abundance (i.e., summer in subtropical or Mediterranean climates and the rainy season in drier tropical climates), phlebovirus activity is continuous. In this situation one sees little illness in the native population, most of whom are already immune, but when a group of nonimmune adults (i.e., tourists, soldiers) enters in the area, an epidemic quickly ensues.[2]

Although more than 40 PF virus serotypes have been described,[2] three virus serotypes (Naples, Sicilian, and Toscana) account for most of the recognized PF cases. This is probably because their sandfly vectors (*Phlebotomus papatasi*, *P. perniciosus*, and *P. perfiliewi*) are highly anthropophilic, readily enter houses, and have a wide geographic distribution in the Mediterranean region and central Asia.[3] In contrast, most of the New World phleboviruses and their vectors have a more focal and sylvan distribution; consequently, PF cases in this region are infrequent and occur mainly in persons who enter forested areas for work or recreation.

After an incubation period of 3–5 days, PF begins suddenly with fever, severe frontal headache, retro-orbital pain, photophobia, malaise, anorexia, nausea, vomiting, and low back pain.[8] The face is often flushed and the conjunctivae are injected, but a true rash is absent. The disease is self-limited, and the symptoms usually disappear within 2–3 days; however, a general feeling of weakness and depression frequently lasts for a week or more after the illness. Marked leukopenia (<4000/μL), consisting of initial lymphopenia, followed by protracted neutropenia, also occurs in PF.[8]

Aseptic meningitis is a relatively common manifestation of Toscana virus infection. Originally described in central Italy, this infection occurs throughout much of the Mediterranean region of Europe and is a frequent cause of summertime meningitis in both adults and children.[9] These cases begin as classic PF, with a nonspecific febrile illness for 2–4 days before the appearance of more serious symptoms, such as nuchal rigidity, positive Kernig's sign, nystagmus, and reduced levels of consciousness.[7] In these cases the hematologic picture is similar to that of classic PF, but the cerebrospinal fluid (CSF) may show increased pressure, but without pleocytosis and with normal glucose and protein levels. The neurologic abnormalities usually resolve in a few days, and most patients recover spontaneously in 1–2 weeks, although headache may persist. The recovery of phleboviruses from patients with PF is uncommon, since the viremia associated with this disease is quite transient (24–36 hours), and most patients do not seek medical care so early. The one exception is patients with neurologic disease due to Toscana virus infection; virus can be recovered from the CSF after it has disappeared from the blood.[6] Culture in Vero cells is the isolation system of choice for most phleboviruses.[2] RT-PCR can also be done on CSF of patients with neurologic symptoms of Toscana virus infection.

A number of serologic techniques can be used for the diagnosis of PF, but each has its limitations. The IgM-capture enzyme-linked immunosorbent assay (ELISA)[10] and plaque reduction neutralization test (PRNT)[2,8,11] are quite specific and sensitive, but one must screen against a variety of phlebovirus serotypes because of their focal and sometimes overlapping distribution. Seroconversion can be demonstrated in paired samples by IgG ELISA and by fluorescent antibody (FA) or hemagglutination-inhibition (HI) tests, but these techniques are not serotype-specific.

Treatment of PF is symptomatic. Except for patients with neurologic symptoms, as in Toscana virus infection, hospitalization is usually unnecessary. The headache associated with PF can be severe, and narcotics are sometimes needed for relief. PF is a self-limited, nonfatal disease, and recovery is complete. One attack of PF confers lifelong immunity against the infecting virus type but not against heterologous serotypes.[8,11] Thus, second cases of the disease can occur among persons living in regions where more than one phlebovirus is active. There are no vaccines for PF. Control measures are directed against the vector and include household spraying with residual insecticides, bednets, and the use of insect repellents.[3]

OROPOUCHE FEVER

Oropouche fever is a midge-borne viral disease that has emerged during the past 50 years as an important public health problem in tropical South America.[12,13] The causative agent, Oropouche virus (genus *Orthobunyavirus*), was first isolated from the blood of a febrile forest worker in Trinidad in 1955. Since 1961, more than 30 outbreaks of Oropouche virus have been reported from the Amazon regions of Brazil and Peru and from Panama. The number of persons affected has varied with each outbreak, but the two largest recorded epidemics (Belem and Manaus, Brazil, in 1980 and 1981) each involved about 100 000 people.[12]

It is postulated that Oropouche virus is maintained in two distinct cycles: (1) an epidemic urban cycle involving the biting midge *Culicoides paraensis*; and (2) a silent maintenance cycle in which forest animals (sloths and possibly monkeys) are the principal vertebrate hosts, and a yet unidentified arthropod serves as the vector.[12] However, the epidemiology of this disease is still not fully elucidated, as it is easily confused with dengue and other acute febrile illnesses, and the true incidence is unknown.

Oropouche fever is characterized by the abrupt onset of fever (up to 40°C), chills, severe headache, mayalgia, arthralgia, anorexia, weakness, dizziness, and photophobia.[12,13] Nausea, vomiting, diarrhea, and epigastric pain may also occur. Some Oropouche fever patients can present with a clinical picture of aseptic meningitis or meningoencephalitis. Rash is rarely present, but leukopenia is a common feature of this disease. The acute clinical illness usually lasts 2–5 days, although a period of asthenia and occasionally dizziness may persist for up to a month. A significant percentage of patients (as high as 60% in some outbreaks) have a recrudescence of their original symptoms within 2–10 days after they become afebrile.[12] The recurrent illness associated with Oropouche fever seems to occur more commonly in persons who quickly resume strenuous activities. No virus can be isolated from the patient's serum during the recurrent illness, and detectable humoral antibodies are usually present.

Oropouche virus can often be recovered from the patient's serum during the first 2–4 days of the disease. The virus can be isolated in newborn mice, adult hamsters, and a variety of mammalian cell cultures. Demonstration of virus-specific antibody can be demonstrated in paired acute and convalescent phase sera by ELISA, IFA, HI, complement fixation (CF), or PRNT. Treatment is symptomatic. No fatalities have been reported with Oropouche fever; and lifelong immunity follows recovery.

There is no vaccine against Oropouche fever. Given our limited knowledge of the maintenance cycle of Oropouche virus, vector control appears to be the best prevention and control strategy. *C. paraensis* is a daytime feeder and, because of its tiny size, readily passes through window screens. Spraying or fogging in and around houses with residual insecticides is of limited value in the control of adult peridomestic populations of this midge vector. Cleaning up rotting vegetation (e.g., banana stalks, decomposing fruit) around houses can help to eliminate *C. paraensis* larval breeding sites. Insect repellent applied to exposed skin also reduces the number of bites.

GROUP C AND GUAMA VIRUS INFECTIONS

Group C and Guama viruses are found throughout the New World tropics and subtropics, including Florida, Mexico, Central America, and the warmer regions of northern South America.[14] At least 25 different virus serotypes have been identified. Most of the serotypes have focal distribution which coincides with forest or forest-fringe habitats, usually in low-lying swampy areas. These viruses are maintained in continuous sylvan cycles involving mosquitoes, mainly *Culex* of the subgenus *Melanoconion*, and small mammals such as rodents and marsupials. Humans are usually infected when they enter the swampy forest habitats where these viruses are endemic and are bitten by infected mosquitoes. Cases are usually sporadic; and because of their nonspecific nature, they are usually not reported, or are misdiagnosed, so their true incidence is unknown.

Persons infected by group C and Guama group viruses develop sudden fever (38–40°C), severe headache, vertigo, myalgia, retro-orbital pain, malaise, and nausea. The fever lasts 2–5 days and is sometimes biphasic. Rash is absent. Patients recover with weakness and anorexia lasting 1 or 2 weeks, but without sequelae.

These viruses can be recovered from patients' sera during the acute febrile phase of the illness. They grow well in a variety of cell cultures and kill newborn mice and hamsters. Antibodies can also be detected in paired acute and convalescent sera by HI, CF, ELISA, IFA, and PRNT. Treatment is nonspecific and supportive. The major risk factor is occupation; avoidance of swampy forest habitats and personal protection against mosquito bites are the only prevention.

BWAMBA, ILESHA, AND TATAGUINE VIRUS INFECTIONS

These three bunyaviruses have been isolated repeatedly from sick persons and mosquitoes in East, Central, and West Africa.[15,16] The diseases associated with them are similar: the acute onset of fever, headache, vertigo, severe mayalgia, and rash, lasting 4–5 days and followed by a week or more of asthenia. No deaths or serious complications have been reported. Most of the mosquito isolations of Bwamba, Ilesha, and Tataguine viruses have been made from *Anopheles* and *Aedes* species.[15] The viruses are thought to be maintained in a mosquito–wild vertebrate cycle, but little other information is available. Given their demonstrated disease potential, wide geographic distribution, and the relatively high antibody rates found in serosurveys among humans in some African countries,[15,16] it seems likely that these agents are of greater health importance to the local populations and to visitors than is currently recognized. But because of the paucity of functioning virus laboratories in Africa and the nonspecific nature of illness associated with them, most of these infections are probably never recognized or reported. Diagnosis can be made by virus isolation from blood during the febrile period or by antibody detection in paired acute and convalescent sera.