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# Lassa, Marburg and Ebola: newly described African fevers

As a result of rapid travel by jet, people can arrive in North America from any part of the world within the incubation period of any infectious disease. While malaria is the most common cause of fever in Africa, there are other newly described fevers that are more contagious and more lethal. Lassa fever is one of them.

Most Canadians had never heard of Lassa fever until August 1976, when the news media described in detail a presumed case in a woman hospitalized in metropolitan Toronto.[1] The woman had never visited Africa; she was returning to Canada after a visit to Europe when she became ill. About the same time a case of Lassa fever was diagnosed in London. The woman from Toronto had had no contact with this individual or any other sick person. However, because her fever and pneumonia did not respond to treatment with antibiotics and because none of the investigations proved diagnostic, a serum sample was sent to the Center for Disease Control in Atlanta, Georgia. The indirect fluorescent test for antibody to Lassa virus was positive; therefore the woman was presumed to have Lassa fever. The hospital was closed temporarily and all contacts were traced and kept under surveillance. Although local, provincial and federal health officials worked hard and cooperated closely on this case, subsequent detailed viral studies failed to isolate the Lassa virus and the diagnosis was never confirmed. As a result, a procedure has been developed for the isolation of the patient and the surveillance of the contacts.

On at least two previous occasions Canadian volunteer workers in rural Africa had been sick with suspected Lassa fever. The decision as to whether to bring the patient home is a difficult one. Because treatment is only supportive and rural African hospitals do not have sophisticated life-supporting facilities it seems humane to bring the patient home to a well equipped hospital. However, by having a patient with a highly contagious condition in Canada the whole population is exposed to a dangerous disease for which there is no preventive vaccine or treatment. On balance it appears wise to transport the sick person in a specially equipped military aircraft to a specially equipped isolation facility at home. Health and Welfare Canada has installed such an isolation unit at the National Defence Medical Centre in Ottawa for patients with dangerous contagious diseases.

Because several thousand Canadians are working in various parts of West Africa at any one time, many Canadian physicians will be called upon to treat febrile patients returning from Africa. It is therefore useful to review the newly identified viral fevers that are generally endemic only in Africa.

In 1969 three missionary nurses contracted a fever that did not respond to treatment with antimalarial agents and antibiotics. They had contracted the disease while nursing febrile patients in Jos, Nigeria. Two of the nurses died and one recovered after a long illness.[2] A virus isolated from the nurses was demonstrated to be a new member of the arenaviruses, of which the lymphocytic choriomeningitis (LCM) virus is the prototype. The arenaviruses are ribonucleic acid viruses and include 10 morphologically similar and serologically related viruses. Four of the arenaviruses are known to cause human disease: LCM, aseptic meningitis; Juno, Argentinian hemorrhagic fever; Machupo, Bolivian hemorrhagic fever; and Lassa, Lassa fever.[3]

Lassa fever is probably not a new disease. Only modern virologic techniques have made the isolation of this

virus possible, but it may be that previous cases of unexplained fever epidemics have been of Lassa fever.[4] Having acquired the virus from rodents, humans spread it by means of blood, secretions and body fluids; hospital personnel have the highest risk of acquiring the infection.

The clinical features of Lassa fever are fever, pharyngitis, abdominal symptoms and, in half the cases, lymphadenopathy, leukopenia and albuminuria.[5] These clinical features are not specific enough to be diagnostic, so a presumptive diagnosis can be made only when there is a history of travel in rural Africa and contact with febrile patients, and when other causes of fever have been excluded. Definitive diagnosis depends on isolation of the virus from blood, urine or other body fluids.[5]

The demonstration of complement-fixing antibodies to Lassa virus antigen is almost certainly diagnostic of Lassa fever. This is especially true when there is a conversion from negative to positive in a paired serum sample. The complement-fixation test, however, is not sensitive enough and may become positive only when the infection is at an advanced stage. The indirect fluorescent antibody test may be more sensitive and may detect antibodies earlier in the course of infection.[6] Increased sensitivity, however, may be accompanied by increased nonspecificity, and antibodies to other arenaviruses, such as the LCM virus, may crossreact with Lassa viral antigen.

In earlier outbreaks the mortality of Lassa fever was reported to be approximately 50%,[7] a figure that subsequently has been reduced. Serologic surveys have shown that there are many subclinical and clinically benign infections, and that Lassa fever is more widespread than has previously been reported.[8,9] In the Sierra Leone outbreak it was estimated that only 1 of 30 patients with infections needed hospitalization, and that the mortality in infected persons was less than 1 in 60.[10] In the most recently published case of Lassa fever imported to the United States the patient had a very mild illness. In none of the 552 contacts kept under surveillance did the illness develop. A serologic survey of the persons at high risk showed no evidence of infection.[11] Hence it can be assumed that Lassa fever is not as lethal and contagious as originally thought. Infections acquired in the laboratory appear to be more virulent. In the United States two persons acquired infection in a laboratory, one of whom died.[12]

The principal reservoir of Lassa virus is rodents, particularly the species *Mastomys natalensis*.[13] This multimammate mouse, the most common and most widespread rodent in Africa south of the Sahara Desert, is an ideal carrier of animal diseases to humans because of its preference for living near human habitations and its exceptionally high propagation rate.[14] This rodent is also an important link in the plague cycle in southern Africa. Lassa virus has been isolated from other rodents, such as *Rattus rattus* and *Mus minutoides*.[13]

In 1967 three simultaneous outbreaks of a severe febrile illness occurred in laboratory workers in Marburg, West Germany, and Belgrade, Yugoslavia. There were 25 primary and 6 secondary cases of infection. The primary infections were all acquired by contact with a consignment of green velvet monkeys from Uganda. The etiologic agent was found to be a virus, previously unknown, that has been named Marburg virus.[15] Subsequent intensive investigations did not reveal the monkeys to be a reservoir of this virus; the reservoir remains unknown.

In late 1976 there was an outbreak of a severe febrile illness with a high mortality in southern Sudan and northern Zaire. It was estimated that in this outbreak there were more than 600 cases and more than 450 deaths. A World Health Organization international commission operating in the endemic areas sent specimens to high security laboratories in England, Belgium and the Center for Disease Control in Atlanta. The virus isolated by all these laboratories was morphologically similar but serologically distinct from Marburg virus. The name Ebola (Ebola is a small river in Zaire) was given to this virus.[16-18]

Clinically patients with Ebola virus infections have a high fever, sore throat, muscular pain, vomiting and diarrhea. Some patients have a skin rash and, in severe cases, hemorrhagic tendencies. The infection is transmitted by direct contact with sick patients and particularly their body fluids. Health workers are at the highest risk. At Maridi Hospital, Sudan, in late 1976, 76 hospital staff became ill with this disease and 41 died. Ebola virus infection is currently believed to be highly contagious and lethal. It is, from preliminary reports, more virulent than Lassa fever. To date no reservoir or vector for Ebola virus has been found, but it is generally accepted that monkeys are not the reservoir.

There is no specific treatment for Lassa, Marburg or Ebola fever. Plasma from patients who have recovered from Lassa fever has been used with some success in Lassa patients. Interferon given to a patient with Ebola virus infection acquired in the laboratory may have helped in the patient's recovery.[19]

Hyperimmune plasma is in limited supply and should be given only to patents proven to have the disease and patients who are critically ill and suspected of having the disease. There is no vaccine for these viral infections.

Experience has shown that malaria is the most common cause of fever in patients who have recently been in Africa. The other common causes, in decreasing likelihood, are respiratory infection, preicteric hepatitis, infective enteritis (caused by *Salmonella* or *Shigella*) and invasive amebiasis.[20] Physicians must now consider these newly described viral infections in their differential diagnosis. It is suggested that all febrile patients who have been in West or Central Africa in the preceding 2 to 3 weeks be considered to have potential Lassa or Ebola fever. Blood smears should be done immediately, and if they are negative for malaria the patient should be isolated in a single room until the probable diagnosis is more certain. Leukopenia (leukocyte count of less than $4.0 \times 10^9$/L) in a febrile patient from West Africa should suggest typhoid or Lassa fever. In either instance the patient should be isolated. If the patient is likely to have Lassa fever it is important to remember that health workers such as physicians, nurses and laboratory technologists in rural West Africa are at the highest risk. A business man or tourist in a large city in Africa who has no contact with sick people is unlikely to have Lassa or Ebola virus infection.

There are, in large Canadian cities, an increasing number of physicians knowledgeable in importation medicine; family physicians and physicians in the emergency rooms of hospitals should not hesitate to seek advice from them. If the diagnosis of Lassa or Ebola fever is considered likely the hospital microbiologist and district public health officer should be notified immediately. They should then arrange for specimens to be sent to a specialized laboratory for serologic tests and viral isolation. At this time consultation should begin with provincial and federal health authorities (such as the Laboratory Centre for Disease Control, health protection branch, Health and Welfare Canada) concerning more strict isolation of the patient, such as transfer to the isolation unit at the National Defence Medical Centre in Ottawa, and surveillance of contacts. At present the definitive diagnosis of Lassa or Ebola viral infection is difficult to make because we do not have a maximum security laboratory. It is hoped that such a facility will be established so that we do not waste valuable time in sending samples to the Center for Disease Control in Atlanta. In the meantime, inactivated viral antigen should be made available to large hospitals for rapid serologic diagnosis.

In addition to the improvement of diagnostic ability, the development of a body of physicians knowledgeable in such exotic diseases and the provision for isolation facilities, plans should be made for the collection and storage of plasma from convalescing patients. The latter should be done with the cooperation of an international agency such as the World Health Organization because it will continue to coordinate efforts in controlling future outbreaks of Lassa, Marburg and Ebola fever. The most urgent need, however, is for the development of effective vaccines.[21] It is hoped that national, international and private charitable agencies will encourage and support scientists to work towards this end.

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