

Arenaviruses

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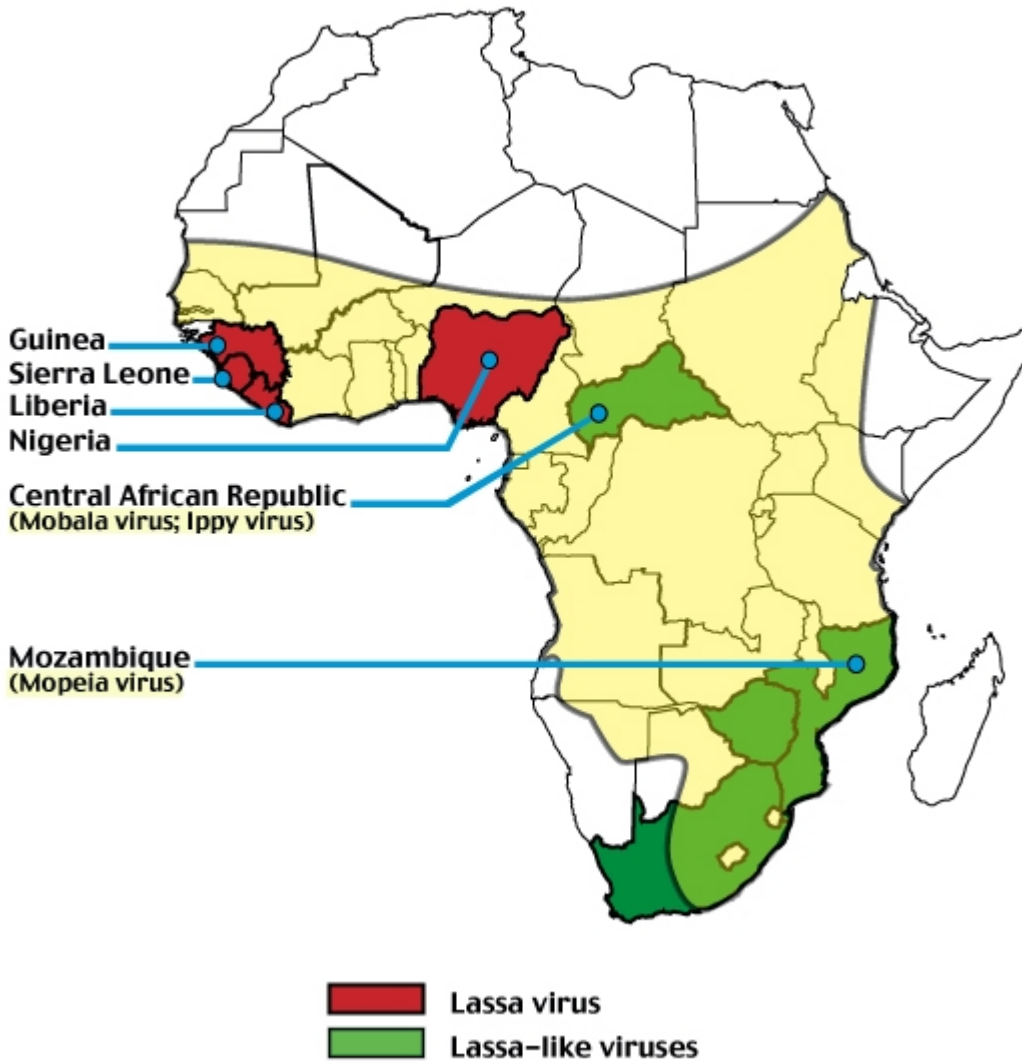
Arenaviruses

Summary

- Arenaviruses: Zoonotic viruses transmitted via rodents mainly, but for some also via secondary person-to-person transmission and nosocomial infection
- Clinically atypical febrile, haemorrhagic, neurological or pulmonary syndrome.
- Ribavirin is used in Lassa fever

General

Map Arenaviruses in Africa (Lassa Fever).



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Mastomys complex

Map arenaviruses - Africa (in yellow: distribution of *Mastomys* mice)

The name of arenaviruses refers to their granular appearance under an electron microscope (L. arena = sand). This structure is created by the inclusion of electron dense host cell ribosomes in the viral envelope. They are RNA viruses, of which the genome consists of a short and a long RNA fragment. Some viruses from this group are pathogenic for humans. Our knowledge concerning these viruses is clearly incomplete. Most arenaviruses have a rodent reservoir. The rodent hosts are chronically infected with the virus, without causing them an obvious illness. Human infection occurs when a

person comes into contact with excretions or other materials contaminated with excretions of the infected rodent via ingestion, via direct contact through broken skin/mucosa or via aerosol transmission. Tacaribe virus was isolated from fruit-eating bats.

Known pathogenic arenaviruses:

1. Lymphocytic choriomeningitis virus
2. Lassa virus (with substrains Josiah, Nigeria, LP, AV)
3. Junin virus
4. Machupo virus
5. Lujo virus

Non-pathogenic arenaviruses and viruses with unknown pathogenicity:

1. Old World: Mopeia, Mobala, Ippy, Acar
2. New World : Tacaribe, Tamiami, Parana, Amapari, Flexal, Pichende, Latino, Oliveros

Incubation time

Nosocomial transmission and transmission via infected body fluids are known for Lassa fever, Ebola and Marburg virus as well as other non-arboviral haemorrhagic fevers. The Bunya-, Filo- and Flaviviruses are cytolytic. They destroy cells particularly endothelial cells. The incubation time is usually less than one week.

Arenaviruses are not cytolytic. They act indirectly by forming antigen-antibody complexes and activating complement. The incubation time tends to be longer than in the other groups.

New Arenaviruses

It is very likely that new viruses will be discovered in the future. An example is Lujo virus, a new member of the family Arenaviridae. This haemorrhagic fever virus was discovered in 2008, when it was responsible for an outbreak in South Africa (the index patient came from Zambia, 5 cases in total). Human disease is characterized by nosocomial transmission and a very high case fatality rate of 80 percent.

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Lymphocytic choriomeningitis virus

The first arenavirus to be isolated was lymphocytic choriomeningitis virus (LCM). It was discovered in 1933 during an epidemic of St Louis encephalitis in the USA. The virus can infect mice. Neonatally infected mice become chronic carriers and excrete the virus for a long time in their urine. The course of the infection is determined by age, immunological resistance, the virus strain and the genetic makeup of the rodent. Both *Mus musculus* and *Mus domesticus* (the common house mouse) can be infected. Other rodents, such as hamsters, which are sometimes kept as pets, can also become infected and can be responsible for transmission. Lymphocytic choriomeningitis virus can also be transmitted via organ transplantation.

In humans it is mainly known for causing an “aseptic” meningitis, with or without fever about 10 days before the meningeal signs appear, though infection is more often without symptoms or a mild febrile illness. LCMV infection in immune compromised patients tends to be severe. Sometimes there is severe damage to the central nervous system. Transient hydrocephalus has been described. Chorioretinitis and congenital hydrocephalus may occur in foetal infection. The cerebrospinal fluid exhibits lymphocytic pleocytosis, an elevated protein content and in 25% of patients there is also reduced sugar. Rarely transverse myelitis, ascending myelitis or bulbar paralysis occur. Some cases of residual deafness have been described after LCM infection. At present, a significant fraction of cases of neonatal mental retardation and blindness remain unexplained. Congenital LCMV infection is an understudied potential cause of a portion of these cases.

There is no specific treatment. There is no vaccine. In general, mortality is less than 1%.

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Lassa fever

Lassa virus

Lassa virus is an arenavirus. There are some subtypes, such as the Josiah, Nigeria, LP and AV strains. The disease “Lassa fever” takes its name from a small town in Nigeria. The disease occurs, endemically, in West Africa: Sierra Leone, Guinea, Liberia and Nigeria, but probably also outside these countries, based on case reports and serosurveys in humans and animals (Ghana, Ivory Coast,

Burkina Faso, Senegal, Mali, Central African Republic). The total number of annual cases is estimated between 100.000 and 300.000 case with 5000 deaths.

Transmission is via ingestion of food infected with urine or faeces of infected peridomestic rats (*Mastomys natalensis* = *Praomys natalensis*). The rat itself exhibits no symptoms. There are many morphologically similar rodents, which differ in karyotype.

Transmission via aerosol has been demonstrated in the laboratory. Person-to-person transmission occurs, as does nosocomial transmission, including due to re-use of needles. Transmission may also occur via sexual intercourse (Lassa virus has been isolated from semen up to 6 weeks after the acute stage).

Isolation and strict barrier nursing are sufficient to prevent transmission in the hospital. Avoidance of contact with rodents is important (especially of food storage areas where these rodents are common). From time to time there are imported cases in Europe and North America.

Clinical aspects

In about 80% of patients, the disease has a mild course. After an incubation period of 7-18 days, infected persons gradually develop a sore throat with an inflammatory exudative pharyngitis, fever, malaise and myalgia, conjunctivitis and swollen eyelids, abdominal pain with or without nausea, vomiting and diarrhoea, cough, dyspnoea and tachypnoea, thoracic pain, pleural fluid and pain in the joints and loins. Oedema of the face may occur. Patients do not die with a clinical picture of DIC [diffuse intravascular coagulation], but with liver necrosis, haemorrhage, shock and pulmonary oedema. Icterus occurs rarely. Diffuse haemorrhages and swelling of the head and neck indicate increased vascular permeability and a poor prognosis. The cerebrospinal fluid is usually normal. After a few weeks pericarditis and/or cerebellar ataxia occur. There is moderate thrombocytopenia, but there is significant and pronounced blood platelet and endothelium dysfunction. Proteinuria is common. Death results from multi-organ failure in about 20% of those hospitalized. In those surviving there is often sensorineural deafness (25%). ARDS is a frequent cause of death in Lassa fever. Spontaneous abortion is a possible complication in pregnancy.

Diagnosis

Diagnosis is suggested via clinical symptoms in West Africa (thoracic pain, fever, haemorrhage, pharyngitis). In Lassa fever, the white cell count tends to be normal. In severe cases, lymphopenia with neutrophilia as well as haemoconcentration can occur. Mild thrombocytopenia can be expected. Confirmation will be obtained via serology (ELISA IgM and/or seroconversion IgG), virus isolation or

RT-PCR [reverse transcriptase polymerase chain reaction] for viral RNA in a high-containment laboratory (urine, blood, throat swab). IFA (indirect fluorescence assay) can be done on serum using a fluorescence microscope using anti-Lassa monoclonal antibodies. Immunoblotting with gel electrophoresis can detect Lassa proteins using specifically labelled antibodies.

Treatment

Patients should be isolated in an intensive care unit. Ribavirin (Virazole®, Rebetol® – caps. 200 mg), a guanosine analogue, administered during the first 6 days of the disease, is effective (30 mg/kg IV loading dose; then 16 mg/kg IV every 6 hours for 4 days, then 8 mg/kg IV every 8 hours for 6 days). Probably it is also beneficial as chemoprophylaxis (direct contacts PO 500 mg QID for 7 days). In practice ribavirin will often not be available. In the West this drug is used as an aerosol for the treatment of severe pulmonary infection with RSV (respiratory syncytial virus). In China it is used in hantavirus epidemics.

Prevention

Contact with rodents and their excreta (especially urine) should be limited as far as possible. Infected patients should be cared for and treated with the necessary caution (barrier nursing) to avoid nosocomial transmission. In experiments it has been possible to protect primates with a vaccinia virus-expressed Lassa virus vaccine. However, vaccines based upon vaccinia constructs might be dangerous in a population with a high seroprevalence of HIV infection. A recombinant vesicular stomatitis virus-based vaccine protected primates from lethal Lassa virus infection. There is no commercial vaccine for humans available.

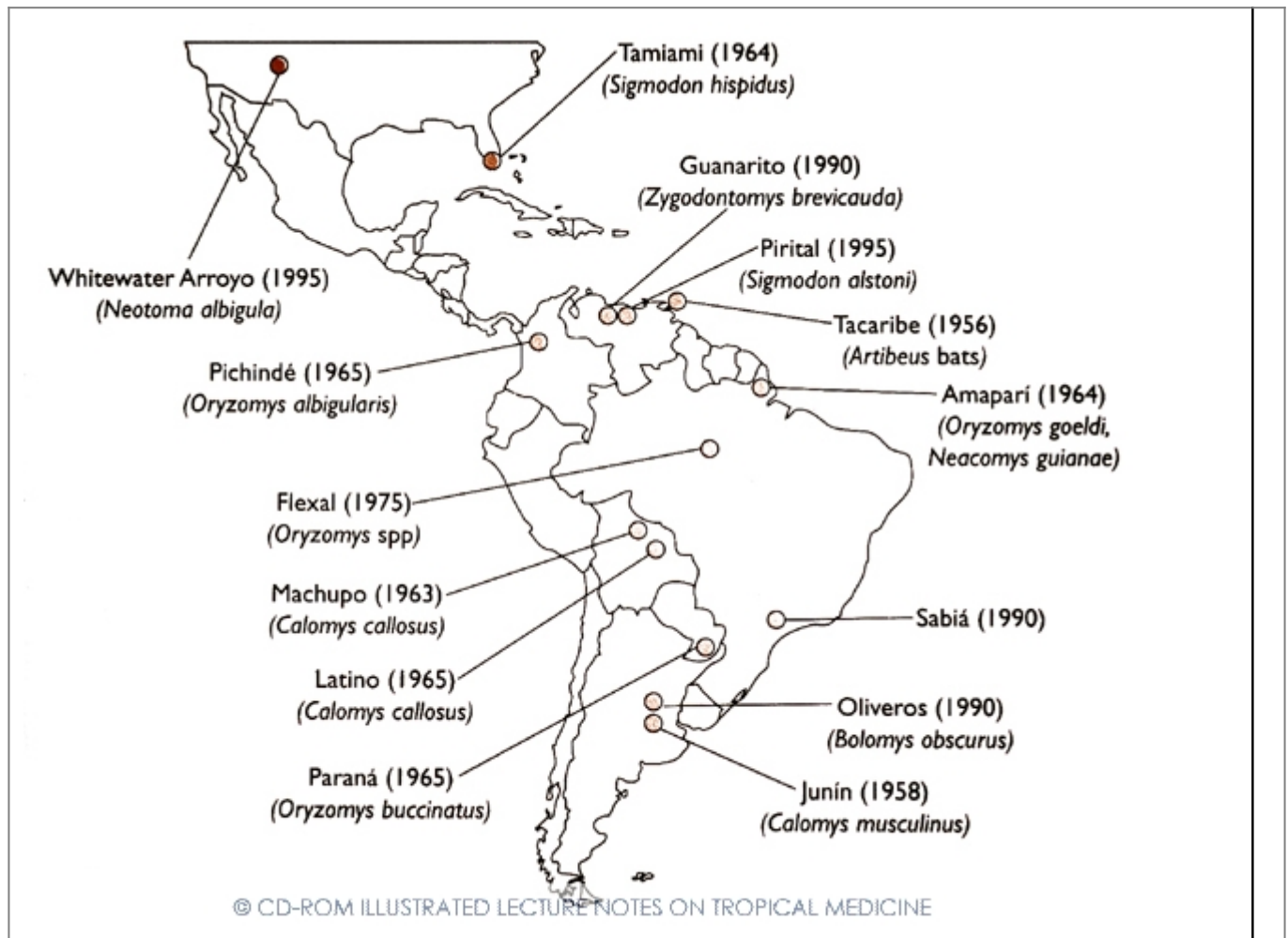
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New World arenaviruses

General

There are at least 16 arenaviruses in the New World, but most of these are not pathogenic for humans. Junin and Machupo virus occur in South America. The viruses were named after places in Argentina and Bolivia. Guanarito virus causes Venezuelan haemorrhagic fever. Sabia virus causes Brazilian haemorrhagic fever. In North America in 1970 the apathogenic Tamiami virus was found in cotton rats in Florida, but otherwise it was thought that arenaviruses did not occur in North America. In 1996 Whitewater Arroyo virus was identified in the USA. The name refers to a place in the state of

New Mexico. It was not known at the time whether this virus was pathogenic or not. In 2000 several people became infected with this virus, with serious consequences. Bear Canyon virus is a third North American arenavirus, the pathogenic capacity of which is to date still unknown.



Map Arenaviruses - New World. Copyright ITM

Transmission

Transmission of Junin and Machupo virus is via rodents (*Calomys musculinus* and *Calomys callosus* respectively) which live in the fields (not peridomestic). Female rodents infected neonatally with Junin or Machupo virus are subfertile. Infection is via inhalation of swirling dust containing dried rodent urine (aerogenic transmission). Infection with Junin virus is seasonal and shows a peak during the harvest in autumn. *Calomys musculinus* has a preference for linear habitats, e.g. hedges and

roadsides. *Calomys callosus* prefers to live in open fields. An outbreak of 1963-64 with 637 cases and 113 deaths was due to a proliferation of the rodents in a Bolivian town. Transmission was stopped by catching or killing the rodents. Many children all over the country gave their pet cats in an emotional gesture to help catch the rodents.

Clinical aspect

Machupo and Junin viruses cause similar clinical pictures. Initially there is a rather slow onset of unspecific malaise and fever, muscle pain, conjunctivitis, nausea, vomiting and sometimes photophobia. Unlike Lassa fever, pharyngitis is not pronounced. Enlarged lymph nodes and pronounced erythema of the face, neck and thorax are common. Thrombocytopenia, leukopenia and albuminuria are generally present. Chest X-ray is usually normal. Machupo and Guanarito virus infections often cause neurological symptoms. Haemorrhage and shock herald a poor prognosis. Whitewater Arroyo virus causes high fever, liver problems, internal haemorrhage and possibly death. Only a few cases of Sabia virus infection have been documented.

Treatment

Physical protection of doctors and nurses is necessary (barrier nursing). Good results have been described with convalescent plasma from survivors, especially if this is administered early. Ribavirin is active in vitro against all arenaviruses. The penetration of ribavirin into the cerebrospinal fluid is very low. Salicylates and intramuscular injections should be avoided. Thrombocytes should be transfused in case of severe thrombocytopenia. In view of the heightened vascular permeability, caution is advised with IV fluid (risk of pulmonary oedema).

Prevention

Sometimes high-risk persons are given ribavirin preventively for two weeks (1.2 g daily PO).