The Arenaviruses

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Family: Arenaviridae

• Single stranded RNA virus
• Enveloped in a lipid (fat) membrane
• Name derived from Latin “arena,” which means “sandy” due to grainy appearance on cross-section
• Reproduction by budding of new particles called virions
Family: Arenaviridae

• 19 distinct viruses; at least 7 pathogenic to humans

• 2 Complexes (Serogroups); both monophyletic
  • Old World (5 members)
    • LCMV-LASV Complex
      • Lymphocytic choriomeningitis virus (LCMV)
      • Lassa virus
  • New World (14 members)
    • Tacaribe Complex
      • Junin, Machupo, Guanarito, Sabia, Pirital

• Pathogenic phenotype appears to have arisen in multiple independent events during virus evolution
Clinical Characteristics

**Old World Arenaviruses**

- Lymphocytic choriomeningitis virus (LCMV)
  - Asymptomatic infection or mild febrile illnesses are common
  - Aseptic meningitis
  - Prenatal infections (abortion, hydrocephalus, chorioretinitis, and mental retardation.

- Lassa Fever
  - Acute, mild to severe febrile illness, +/- hemorrhagic or neurologic manifestations; deafness a sequelae in 20%

Source: Bowen MD, 1997
Clinical Characteristics

• New World
  • South American Hemorrhagic Fevers (Junin, Machupo, Guanarito, Sabia, Pirital)
    • Hypotension, shock, bleeding, neurologic symptoms, multisystem failure
  • North American Arenaviruses?

Clinical Characteristics

• Incubation 10-14 days
• Case fatality 15% (Lassa) to 30% (South American HF)
• Viremia during acute illness
• Antibodies may not be present in acute illness
• Treatment with Ribavirin (limited availability)
• Vaccination?
Reservoirs

• Rodent hosts
  • Family: Muridae
    • 2 subfamilies important reservoirs of arenaviruses
      • Murinae - old world rats and mice
      • Sigmodontinae - new world rats and mice
  • Evidence of cospeciation?

• Bat (Chiroptera) hosts
  • Tacaribe isolated in Trinidad from bats

Old World Arenaviruses

LCMV/Lassa Complex

• Lymphocytic choriomeningitis virus (LCMV) is associated with the house mouse

• Found in Europe and the Americas, including the United States, Australia, and Japan.

• Seroprevalence of LCMV infection among humans in urban areas ranges from 2% to 10%.
Old World Arenaviruses

LCMV/Lassa Complex

• Lymphocytic choriomeningitis virus (LCMV) is associated with the house mouse

• Found in Europe and the Americas, including the United States
• Presents as aseptic meningitis, encephalitis or meningoencephalitis.

House mouse (Mus musculus)

Old World Arenaviruses

LCMV/Lassa Complex

• The illness discovered in 1969 when two missionary nurses died in Nigeria, West Africa. Lassa virus, named after the town in Nigeria where the first cases originated.

• Lassa virus is associated with themultimammate rat in West Africa
• It is recognized in Guinea, Liberia, Sierra Leone, as well as Nigeria.

Multimammate rat (Mastomys sp.)

Lassa virus electron micrograph.
Source: C.S. Goldsmith and M. Bowen (CDC).
Old World Arenaviruses

LCMV/Lassa Complex

• 100,000 to 300,000 Lassa virus infections and 5,000 deaths per year

• Mild or no observable symptoms in about 80% of people infected with the virus, the remaining 20% have a severe multisystem disease.

• Occasional epidemics, during which the case-fatality rate can reach 50%.

Multimammate rat (Mastomys sp.)

Lassa virus electron micrograph.
Source: C.S. Goldsmith and M. Bowen (CDC).

New World Arenaviruses

Tacaribe Complex

• Tamiami virus associated with cotton rats in Southern Florida

• Unknown if pathogenic to humans

Cotton rat (Sigmodon hispidus)
New World Arenaviruses

Tacaribe Complex

• Tacaribe virus isolated from bats in Trinidad

Bat (Order: Chiroptera)

Transmission

• Each virus usually associated with a particular rodent host species

• Transmission between rodents probably by fighting and bites in adults; vertical transmission for some old world viruses

• Chronic/persistent infection in rodents with virus shed in urine and feces of infected hosts; +/- illness in rodent hosts
Transmission

• Transmission to humans by inhalation of contaminated aerosols, ingestion of contaminated food, or by direct contact of abraded skin with infected rodent secretions or excretion

• Person-to-person transmission for some pathogenic strains (Lassa, Machupo viruses)

History of Arenaviruses in North America

• 1933 Lymphocytic choriomeningitis virus (LCMV) isolated from house mice during a study of an epidemic of St. Louis encephalitis. Although not the cause of the outbreak, LCMV was found to be a cause of aseptic (nonbacterial) meningitis.

• 1970 Characterization of Tamiami virus associated with cotton rats in Southern Florida (Calisher CH)

• 1995 Sabia laboratory accident (Connecticut)
• 1996 First evidence of woodrat-associated arenavirus (Kosoy MY)
• 1996 Whitewater Arroyo virus isolated from white throated woodrats from New Mexico (Fulhorst C)
• 2000 First evidence of Peromyscus-associated arenaviruses in California (Bennett SG)
### Arenavirus antibody in rodents from Southern and Western United States

<table>
<thead>
<tr>
<th>Species</th>
<th>Location*</th>
<th>% Positive**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Murminae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mus musculus</em></td>
<td>FL, TX</td>
<td>2/219 (0.9%)</td>
</tr>
<tr>
<td><strong>Sigmodontinae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neotoma albigula</em></td>
<td>AZ, CO, NM</td>
<td>28/395 (7.1%)</td>
</tr>
<tr>
<td><em>Neotoma fuscipes</em></td>
<td>CA</td>
<td>17/96 (17.7%)</td>
</tr>
<tr>
<td><em>Neotoma lepida</em></td>
<td>CA</td>
<td>1/104 (1%)</td>
</tr>
<tr>
<td><em>Neotoma mexicana</em></td>
<td>AZ, NM, UT</td>
<td>7/78 (9%)</td>
</tr>
<tr>
<td><em>Neotoma stephensi</em></td>
<td>AZ, NM</td>
<td>3/26 (11.5%)</td>
</tr>
<tr>
<td><em>Oryzomys palustris</em></td>
<td>FL</td>
<td>5/82 (6.1%)</td>
</tr>
<tr>
<td><em>Sigmodon hispidus</em></td>
<td>FL</td>
<td>157/1041 (15.2%)</td>
</tr>
</tbody>
</table>

*Location of seropositive rodents
**Serologic (IFA) test for antibodies to Tamiami, Pichinde, Junin, LCMV.

Source: Kosoy MY, 1996

### Whitewater Arroyo Virus

- Isolation and characterization of arenavirus associated with *Neotoma albigula* from New Mexico
- Nucleocapsid protein gene sequence analysis and antigenic characterization
- Novel arenavirus most closely related to Tamiami virus (Group A)
- Proposed name Whitewater Arroyo virus

*Source: Fulhorst, 1996*
Phylogenetic Analysis of Arenaviruses

Old World

New World

Group A

Group C

Group B

Source: Bowen MD, 1997

Distribution of Known New World Arenaviruses in the United States

Source: C. Fulhorst, personal comm.

- Tamiami
- Whitewater Arroyo (WWA)
- WWA & Bear Canyon
Arenaviruses in California

• Serosurvey conducted 1993-1994 in 16 southern and western states including California (Butte, El Dorado, Kern, Los Angeles, Riverside, San Diego, Siskiyou, and Ventura Counties)

  • Neotoma fuscipes (dusky-footed woodrat)
    • 9/57 (15.8%) positive in San Diego County
    • 8/28 (28.6%) positive in Ventura County

  • Neotoma lepida (desert woodrat)
    • 1/37 (2.7%) positive in San Diego County

Source: Kosoy MY, 1996

Arenaviruses in California

• Serosurvey conducted 1995-1998 in Orange, San Diego, and Los Angeles Counties

  • Neotoma spp.
    • Whitewater Arroyo-like virus

  • Peromyscus spp.
    • Bear Canyon virus (proposed name)

Source: Bennett, 2000
## Arenavirus antibody in rodents from California

<table>
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<tr>
<th>Species</th>
<th>Common Name</th>
<th>% Positive*</th>
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<tr>
<td>Neotoma fuscipes</td>
<td>Dusky-footed woodrat</td>
<td>8/103 (7.8%)</td>
</tr>
<tr>
<td>Neotoma lepida</td>
<td>Dessert woodrat</td>
<td>1/180 (0.6%)</td>
</tr>
<tr>
<td>Peromyscus boylii</td>
<td>Brush mouse</td>
<td>1/32 (3.1%)</td>
</tr>
<tr>
<td>Peromyscus californicus</td>
<td>California mouse</td>
<td>8/73 (11%)</td>
</tr>
<tr>
<td>Peromyscus eremicus</td>
<td>Cactus mouse</td>
<td>1/85 (1.2%)</td>
</tr>
<tr>
<td>Peromyscus maniculatus</td>
<td>Deer mouse</td>
<td>30/353 (8.5%)</td>
</tr>
<tr>
<td>Reithrodontomys megalotis</td>
<td>Harvest mouse</td>
<td>6/268 (2.2%)</td>
</tr>
</tbody>
</table>

*Serologic (ELISA) test for antibodies to Whitewater Arroyo virus (WWA) or Amapari virus. Rodents collected from Orange, San Diego, and Los Angeles Counties.

Source: Bennett SG, 2000
Desert woodrat (*Neotoma lepida*)

Deer mouse (*Peromyscus maniculatus*)
Human Infection in U.S.?

- Surveillance for LCMV through the California Encephalitis Project (Viral and Rickettsial Disease Laboratory, California Department of Health Services)

- Suspect human case investigated in September 1999
  - 52 yo female resident of Riverside and Los Angeles Counties
  - Sudden onset of febrile illness in June 1999, progressing to multisystem failure and death
  - Autopsy revealed hemorrhagic manifestations consistent with a viral illness; negative test results for numerous agents
  - Positive RT-PCR on serum, tissues negative (in poor condition) at University of Texas Medical Branch
  - Patient spent most of month before onset in Palm Desert, Riverside County

Source: Bennett, 2000
Human Infection in U.S.?

• Serosurvey of persons who work with rodents (mammologists, vector control technicians, biologists, etc.)
  
  • 1,452 tested
    • <0.5% positive for Sin Nombre virus
    • 5.2% positive for arenavirus(s)
      • 2.5% LCMV
      • 2.5% WWA
  
  • At least a 10 fold lifetime risk of exposure to arenavirus vs. hantavirus

Source: Fulhorst C, personal comm.

Summary

• Arenaviruses are geographically widespread in the southern and western United States

• New World arenaviruses are naturally associated with the rodent genuses Sigmondon, Neotoma and Peromyscus

• Geographical range of each arenavirus may be in only part of the range of its host

• Existence of multiple species within one genus carrying arenaviruses may represent spillover into sympatic species or may suggest there are multiple arenaviruses not yet characterized
Public Health Implications

• Pathogenic arenaviruses frequently associated with severe illnesses and relatively high case fatality rates or sequelae

• Domestic and peridomestic rodent species may represent higher risk for human exposure to North American arenaviruses
  • *Mus musculus*
  • *Peromyscus maniculatus*
  • *Neotoma fuscipes*
Use Safety Precautions

When cleaning in areas infested with rodents
- Wear rubber gloves
- Don't stir up and breathe dust
- Wet contaminated areas with disinfectant
- Dispose of dead animals properly
- Disinfect used gloves

- When enjoying outdoor activities
  - Avoid contact with rodents
  - Stay away from rodent burrows or nests
  - Keep campsite clean and food tightly sealed
  - Open unused cabins up and air out before entering or cleaning
Future Directions

• Expand serologic surveillance for arenaviruses in California, including Northern California

• Isolate and characterize virus(es) from seropositive Neotoma spp. and Peromyscus spp.
  • Kidney and brain best tissues for isolation

• Surveillance for human cases
  • California Encephalitis Project

• Public health implications?
References


