Hemorrhagic Fever Viruses

Rabindran

Dr. Rabindran, Consultant Neonatologist, Billroth Hospital, Chennai

Address for Correspondence: Dr Rabindran, E mail: rabindranindia@yahoo.co.in

Abstract

Viruses causing hemorrhagic fever are broadly classified into five families as Arenaviridae, Bunyaviridae, Filoviridae, Flaviviridae & Rhabdoviridae. Some of them like Ebola virus can spread through aerosols and are considered as potential biological weapons. Most of their reservoirs are found in animals like rodents. Some of them are tick-borne and maintain a cycle of tick-mammal-tick cycle while others like dengue & yellow fever are mosquito borne. Human to human transmission has also been reported for some viruses. Those infected manifest with typical viral prodrome initially & have characteristic hemorrhagic manifestations during the first or second week of illness. They present with leukopenia, deranged coagulation profile and altered liver enzymes. Vaccines are available for a few viruses & ribavirin shows promising results in some cases. Extensive research is being carried for newer therapies for these hemorrhagic fevers which present with periodic epidemics. Prevention of the disease is possible through arthropod control, mosquito nets, barrier nursing & avoidance of close contact with infected people.

Key words: hemorrhagic fever, mild hypotension, myalgias.

Introduction

Hemorrhagic fever (HF) viruses are simple RNA viruses with lipid envelopes. Five families have been recognised. 1. Arenaviridae: Old World arenaviruses: Lassa virus (Lassa fever), Lujo virus, Lymphocytic choriomeningitis virus (meningitis, encephalitis, congenital fetal infection in normal hosts, hemorrhagic fever in organ transplant recipients). New World arenaviruses: Junin (Argentine hemorrhagic fever), Machupo (Bolivian hemorrhagic fever), Guanarito (Venezuelan hemorrhagic fever), Sabia (Brazilian hemorrhagic fever), Chapare virus (Bolivia), Whitewater Arroyo virus. 2. Bunyaviridae: Phlebo (Rift Valley fever), Nairo (Crimean-Congo Haemorrhagic Fever), Hanta (Hantaan hemorrhagic fever, hemorrhagic fever with renal syndrome), California encephalitis, Garissa, Ilesha 3. Filoviridae: Ebola, Marburg, Cuevavirus, (species Lloviucuevavirus; Lloviu virus) 4. Flaviviridae: Dengue, Yellow fever, Omsk haemorrhagic fever virus, Kyasanur forest disease virus (variants- Alkhumra, Nanjianyn), West Nile virus. 5. Rhabdoviridae: Hemorrhagic fever in Congo[1]. This virus is unrelated to previously known Rhabdoviruses. They are virulent & some are highly infectious (filoviruses&arenaviruses) with person-to-person transmission from direct contact with infected blood & body secretions. Working Group for Civilian Biodefense considers some HF viruses as potential biological weapons based on risk of morbidity & mortality, feasibility of production & ability to cause infection through aerosol dissemination. These include Ebola, Marburg, Lassa fever, New World arenaviruses, Rift Valley fever, yellow fever, Omsk hemorrhagic fever & Kyasanur Forest disease [2].

Clinical Features of Viral HF

Early signs include High fever, headache, malaise, fatigue, arthralgias / myalgias, prostration, nausea, abdominal pain, nonbloody diarrhea, mild hypotension, relative bradycardia, tachypnea, conjunctival involvement, pharyngitis, rash or flushing. Over next 1-2 weeks it progresses to Hemorrhagic manifestations (petechiae, hemorrhagic / purpuric rash, epistaxis, hematemesis, melena, heoptysis, hematochezia, hematuria), CNS dysfunction (delirium, convulsions, cerebellar signs, coma), Hepatic involvement (jaundice, hepatitis). Hemorrhagic manifestations occur as a result of thrombocytopenia or severe platelet dysfunction along with endothelial dysfunction. HF viruses can cause necrosis & hemorrhage in most organs;
however hepatic involvement is particularly prominent. The complications include Shock, DIC, multi-system organ failure, Illness-induced abortion in pregnant women, Transverse myelitis, Uveitis, Pericarditis, Orchitis, Parotitis, Pancreatitis, Hearing /vision loss & Impaired motor coordination.

Laboratory Findings
Leukopenia (except in Lassa), Leukocytosis, Thrombocytopenia, Elevated liver enzymes, Anemia/hemoconcentration, Coagulation abnormalities (prolonged bleeding time, prothrombin time & activated partial thromboplastin time, elevated fibrin degradation products & increased fibrinogen), proteinuria, hematuria, oliguria & azotemia.

Arena Virus
Arenaviruses are spherical / pleomorphic virions, generally 110-130 nm in diameter. Its genome contains single-stranded RNA with 2 segments (both ambisense) measuring 11 kbp. Viral particles contain host ribosomes, which appear as dense granules 20–25 nm in diameter & give viruses "sandy" appearance {Latin word for sand-Arenosos}[3]. About 20 known species are taxonomically divided into Old World & New World (Tacaribe complex) groups [4]. They have associations with rodent hosts & humans become infected when exposed to these rodents or their excreta [5]. Frequent nosocomial transmission has been reported for Lassa fever & Ribavirin has been used for treatment / prophylaxis [6]. An attenuated recombinant vaccine produced protective immune responses in non-human primates [7]. Heparin, Vitamin K, coagulation factor replacement & blood transfusions have been effective in lessening / stopping hemorrhage in some cases.

Bunyaviridae
Bunyaviridae contains about 41 different tropical viruses. They are spherical, lipid membrane-enclosed RNA viruses with glycosylated envelope proteins. They measure between 80 - 120 nm [8]. They contain a single negative strand of RNA organized into 3 segments: large, medium & small segments, which code for the virus nucleocapsid, glycoproteins & polymerase proteins, respectively[9]. The glycoproteins determine cell tropism, host pathogenicity & are sites for viral neutralization by antibody [10]. Factors associated with human disease are medium segment-encoded polyproteins that contain a mucin-like domain & a furin cleavage site [11], which have been implicated in causing endothelial damage, cellular cytotoxicity & interferon antagonism [12]. They exert a direct effect on host gene regulation during infection, as evidenced by the hantaviruses’ ability to suppress cellular interferon responses [13].

Hantavirus
More than 20 genotypes of genus Hantavirus are maintained in the environment by specific rodent species[14]. Specific viruses include Hantaan, Puumala, Seoul, Dobrava Belgrade & Saarema viruses [11]. They cause Hemorrhagic fever with renal syndrome. Rodent is the reservoir & human infection occurs through aerosolized rodent urine.

Nairovirus
Nairovirus is enveloped & possesses a tripartite, negative sense, single-stranded RNA genome [8].All 32 members of Nairovirus genus are transmitted by Argasid/Ixodid ticks, but only 3 cause human disease: Dugbe, Nairobi sheep viruses & Crimean-Congo Haemorrhagic Fever (CCHF). CCHF virus has Tick-mammal-tick cycle & humans are infected from tick bite or contact with slaughtered ruminants.A suckling mouse brain, formalin-inactivated vaccine has been used [15]. High-dose corticosteroids, immune globulin intravenous & fresh frozen plasma have been reported to be successful in CCHF [16]. Ribavirin given for postexposure prophylaxis prevents death in CCHF [17].

Phlebovirus
Phlebovirus causes Rift Valley fever. Mosquito transmission occurs with amplification through cattle & sheep; humans are infected through mosquito bite or exposure to infected tissues of sheep, goats & cattle. Possible consumption of raw milk from infected animals also occurs. Vaccine is available as investigational new drug [18]. Interferon alpha has been useful in some cases [19].

Filovirus
Filovirus are uniquely structured virus having a rope-like, filamentous appearance {Latin word for thread-Filo}. The virions consist of a helical nucleocapsid of closely associated RNA & protein with a tight-fitting envelope. Genomes are composed of a single segment of negative-sense RNA of approximately 19 kilobases [20]. In addition to genetic heterogeneity, they are differentiated by epidemiological & clinical features [21]. Because they cause hemorrhagic fevers with high
mortality rates & are transmissible by the airborne route, they are classified as Biosafety Level 4 agents. They can be diagnosed by detecting antigens with ELISA/ immunostaining & by detecting viral RNA with RT-PCR.

**Ebola Virus**

Ebola virus genome consists of a single 19 kb strand of negative sense RNA with seven viral genes that are transcribed by the viral RNA dependent RNA polymerase present in the virion. The single strand of RNA is covered by helically arranged viral nucleoproteins NP & VP30, which are linked by matrix proteins VP24 & VP4 to the lipid bilayer that coats the virion [22]. Because of a lack of serological cross-reactivity & differences in structure & genomic sequence, Ebola virus & Marburg virus have been classified as separate genera. Currently the genus Ebolavirus contains five recognized viral species: Zaire ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus (formerly Cote d’Ivoire ebolavirus), Reston ebolavirus & Bundibugyoebolavirus [23]. Fruit bat is the reservoir for some strains (Zaire). Primates (Reston, Côte d’Ivoire) & pigs (Reston) have been infected with other strains. Humans acquire infection from direct contact with deceased Ebola patients. Transmission occurs mostly through direct contact of broken skin or unprotected mucous membranes with virus-containing body fluids from an infected person [24]. In early epidemics, the re-use of non-sterile injections was responsible for many healthcare associated transmissions. The most infectious body fluids are blood, feces & vomitus. Infectious virus has also been detected in urine, semen, saliva, aqueous humor, vaginal fluid & breast milk [25, 26, 27]. The main confirmatory test for Ebola virus infection is a positive Ebola RT-PCR. ELISA though has high specificity is not universally available. Ebola specific IgM & IgG antibodies are useful in later stages of infection [28].

Treatment options under trial include 1) ZMapp- a combination of three humanised monoclonal antibodies targeted at three Ebola virus glycoprotein epitopes [29]; 2) TKM-Ebola - interfering RNAs that target Ebola virus RNA polymerase L [29]; 3) Brincidofovir [30]; 4) Favipiravir- inhibits viral RNA dependent RNA polymerase [30]; 5) BCX-4430 - an adenosine inhibitors viral RNA dependent RNA polymerase [31]; 6) AVI-7537 - antisense phosphorodiamidatemorpholino oligomers - targets the Ebola virus VP24 gene [32]. Amiodarone, clomiphene, and chloroquine shown to inhibit Ebola virus interactions with human cells in models [33]. Two experimental vaccines are currently undergoing trials [34]: cAd3-ZEBOV is a chimpanzee derived adenovirus vector with an Ebola virus gene inserted [35]. rVSV-ZEBOV is an attenuated vesicular stomatitis virus with one of its genes replaced by an Ebola virus gene. A Phase I clinical trial for an Ebola DNA vaccine was safe and produced an immune response in humans. Treatment with small interfering RNAs (siRNAs) produced protective immune response in an animal model (guinea pigs) [36]. Novel treatment studies using positively-charged phosphorodiamidatemorpholino oligomers demonstrate protection of monkeys infected with Ebola and Marburg viruses [37]. Studies of high-dose mannose-binding lectin therapy in mice suggest a promising future therapeutic modality for Ebola infection. [38,39].

**Marburg Virus**

Marburgvirus contains a single species, Marburg virus (formerly Lake Victoria Marburg virus) & two individual viruses, Marburg virus & Ravn virus. Similar to Ebola the reservoir is Fruit bat & Primates may be a source for index case infection. Nosocomial spread occurs to humans. ELISA, PCR & virus isolation can be used for confirmation.

**Flaviviridae**

Flaviviridaefamily [Latin word for yellow-flavus] contains more than 70 species [40] out of which 30 are known to cause human disease. They are small (40-50 nm), spherical with a lipid envelope studded with glycoproteins. The flavivirus genome is approximately 11,000 bases long & is made up of 3 structural & 7 nonstructural proteins. There are 3 major complexes within this family namely tick-borne encephalitis virus, Japanese encephalitis virus & dengue virus. All flaviviruses have common group epitopes on their envelope protein which result in extensive cross-reactions in serologic tests.

**Dengue virus**

Dengue virus has a single-strand, positive-sense, RNA genome coding for capsid, membrane, envelope proteins & seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b & NS5) [41]. They exhibit substantial genetic diversity, exemplified by the existence of four distinct serotypes (DEN-1–4) [41]. Five basic serologic tests have been routinely used for diagnosis of dengue infection; hemagglutination-inhibition, complement fixation, neutralization test, IgMcapture ELISA (MAC-ELISA) & indirect Ig G
ELISA [42]. Promising candidate attenuated vaccine viruses have been developed [43].

**Yellow Fever Virus**

Yellow fever (YF) is a mosquito-borne (Aedes aegypti) infection. Up to 50% of hemorrhagic-fever-related mortality worldwide can be attributed to YF [44]. Laboratory infections occur through parenteral exposure or aerosols. Vertical transmission from mother to infant & through breastfeeding occurs. A combination of DEET insect repellant (at least 30%) applied to the skin & permethrin insecticide applied to the clothing, both worn during the day, is an important means of preventing bites from mosquitoes carrying DF or YF. Vaccine- Rockefeller Foundation laboratories (New York) developed the 17D live, attenuated, YF vaccine in the 1930s [45], a single dose of which provides nearly complete protection for at least 10 years. A two-dose regimen of XRX-001 induced neutralizing antibodies in a high percentage of subjects [44].

**Omsk Hemorrhagic Fever**

This viral spread occurs through an unidentified cycle involving ticks, muskrats & voles. Omsk hemorrhagic fever virus can be transmitted through the milk of infected goats or sheep and has been isolated from aquatic animals and water, suggesting that the virus is relatively stable in the environment.

**Kyasanur Forest Disease Virus**

The virus spreads through tick-mammal-tick cycle. Rodents, bats & monkeys appear to be amplifying hosts. A formalin inactivated vaccine is licensed for use in endemic areas [46]. Alkhurma HF virus is a variant of Kyasanur Forest disease virus found in Saudi Arabia [47]. Nanjianyin virus was identified in China is again considered a variant of Kyasanur Forest disease virus.

**Management of Viral Hemorrhagic Fever**

Supportive care, including careful maintenance of fluid and electrolyte balance & circulatory volume is essential. Mechanical ventilation, dialysis & appropriate therapy for secondary infections is indicated. Treatment of othersuspected causes like bacterial sepsis, should not be withheld while awaiting confirmation/exclusion of diagnosis of VHF. Anticoagulant therapies, aspirin, nonsteroidal anti-inflammatory medications & intramuscular injections are contraindicated. Researchers are studying the possibility of targeting tissue factor (TF) which is a protein that activates the coagulation process, blockade of which assists the body's immune response to HF viruses. Recombinant nematode anticoagulant protein c2 (a known inhibitor of tissue factor initiated blood coagulation) & Recombinant human-activated protein C (currently licensed treatment of sepsis) are being studied.

**Ribavirin Therapy**

Ribavirin is recommended for: (1) suspect or probable cases of VHF of unknown viral type (2) suspect, probable, or confirmed cases caused by an Arenavirus or Bunyavirus. Ribavirin has shown in vitro & in vivo activity against Arenaviruses (Lassa fever, New World hemorrhagic fevers) & Bunyaviruses (Rift Valley fever). It has shown no activity against & is not recommended for Filoviruses (Ebola & Marburg hemorrhagic fever) or Flaviviruses (Yellow fever, Kyasanur Forest disease, Omsk hemorrhagic fever). Passive immunotherapy with convalescent human plasma has been used & was effective in Argentine HF (Junin) [2].

**Disease Prevention**

Because many of the hosts that carry HF viruses are rodents, disease prevention efforts include controlling rodent populations, discouraging rodents from entry into homes or workplaces & encouraging safe cleanup of rodent nests & droppings. For HF viruses spread by arthropod vectors, prevention is by community-wide insect & arthropod control. People should use insect repellant, proper clothing, bednets, window screens & other insect barriers to avoid being bitten. For those HF viruses transmitted from one person to another, avoiding close physical contact with infected people & their body fluids is mandatory. Barrier nursing or infection control techniques include isolating infected individuals & wearing protective clothing. Other infection control recommendations include proper use, disinfection, disposal of instruments & equipment used in treating or caring for patients with VHF, such as needles & thermometers.

**Funding: Nil. Conflict of interest: Nil**

**Permission from IRB: Yes**

**References**


33. Turone F. Doctors trial amiodarone for Ebola in Sierra Leone. BMJ 2014; 349 . doi: http://dx.doi.org/10.1136/bmj.g7198


How to cite this article?