Viral hemorrhagic fever

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Viral hemorrhagic fevers (**VHFs**) are a diverse group of animal and human illnesses in which fever and hemorrhage are caused by a viral infection. VHFs may be caused by five distinct families of RNA viruses: the families *Arenaviridae*, *Filoviridae*, *Bunyaviridae*, *Flaviviridae*, and *Rhabdoviridae*. All types of VHF are characterized by fever and bleeding disorders and all can progress to high fever, shock and death in many cases. Some of the VHF agents cause relatively mild illnesses, such as the Scandinavian *nephropathia epidemica* (a Hantavirus), while others, such as Ebola virus, can cause severe, life-threatening disease.

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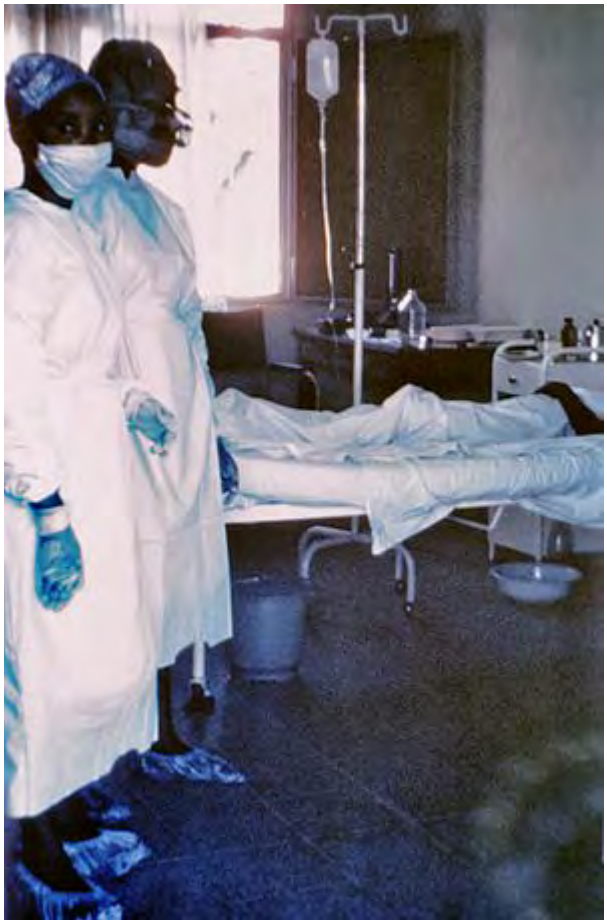

Two nurses standing near Mayinga N'Seka, a nurse with Ebola virus disease in the 1976 outbreak in Zaire. N'Seka died a few days later due to severe internal hemorrhage.

Classification and external resources

Specialty	Infectious disease
ICD-10	A90 (http://apps.who.int/classifications/icd10/browse/2016/en#/A90) -A99 (http://apps.who.int/classifications/icd10/browse/2016/en#/A99)
eMedicine	article/830594 (http://emedicine.medscape.com/article/830594-overview)
MeSH	D006482 (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&term=D006482)

Signs and symptoms of VHFs include (by definition) fever and increased susceptibility to bleeding (bleeding diathesis). Manifestations of VHF often also include flushing of the face and chest, small red or purple spots (petechiae), bleeding, swelling caused by edema, low blood pressure (hypotension), and shock. Malaise, muscle pain, headache, vomiting, and diarrhea occur frequently. The severity of symptoms varies with the type of virus. The "VHF syndrome" (capillary leak, bleeding diathesis, and circulatory compromise leading to shock) appears in a majority of people with filovirus hemorrhagic fevers (e.g., Ebola and Marburg virus), Crimean–Congo hemorrhagic fever (CCHF), and the South American hemorrhagic fevers caused by arenaviruses, but only in a small minority of patients with dengue, Rift Valley fever, and Lassa fever.

Causes

Five families of RNA viruses have been recognised as being able to cause hemorrhagic fevers.

- The family ***Arenaviridae*** include the viruses responsible for Lassa fever (Lassa virus), Lujo virus, Argentine (Junin virus), Bolivian (Machupo virus), Brazilian (Sabiá virus) and Venezuelan (Guanarito virus) hemorrhagic fevers.
- The family ***Bunyaviridae*** include the members of the *Hantavirus* genus that cause hemorrhagic fever with renal syndrome (HFRS), the Crimean-Congo hemorrhagic fever (CCHF) virus from the *Nairovirus* genus, Garissa virus and Ilesha virus from the *Orthobunyavirus* and the Rift Valley fever (RVF) virus from the *Phlebovirus* genus.
- The family ***Filoviridae*** include Ebola virus and Marburg virus.
- The family ***Flaviviridae*** include dengue, yellow fever, and two viruses in the tick-borne encephalitis group that cause VHF: Omsk hemorrhagic fever virus and Kyasanur Forest disease virus.
- In September 2012 scientists writing in the journal PLOS Pathogens reported the isolation of a member of the ***Rhabdoviridae*** responsible for 2 fatal and 2 non-fatal cases of hemorrhagic fever in the Bas-Congo district of the Democratic Republic of Congo. The non-fatal cases occurred in healthcare workers involved in the treatment of the other two, suggesting the possibility of person-to-person transmission.[1] This virus appears to be unrelated to previously known Rhabdoviruses.

Pathophysiology

Different hemorrhagic fever viruses act on the body in different ways, resulting in different symptoms. In most VHFs, it is likely that several mechanisms contribute to symptoms, including liver damage, disseminated intravascular coagulation (DIC), and bone marrow dysfunction. In DIC, small blood clots form in blood vessels throughout the body, removing platelets necessary for clotting from the bloodstream and reducing clotting ability. DIC is thought to cause bleeding in Rift Valley, Marburg, and Ebola fevers. For filoviral hemorrhagic fevers, there are four general mechanisms for pathogensis. The first mechanism is dissemination of virus due to suppressed responses by macrophages and dendritic cell (antigen presenting cells). The second mechanism is prevention of antigen specific immune response. The third mechanism is apoptosis of lymphocytes. The fourth mechanism is when infected macrophages interact with toxic cytokines, leading to diapedesis and coagulation deficiency. From the vascular perspective, the virus will infect macrophages, leading to the reorganization of the VE-cadherin catenin

complex (a protein important in cell adhesion). This reorganization creates intercellular gaps in endothelial cells. The gaps lead to increased endothelial permeability and allow blood to escape from the vascular circulatory system.

The reasons for variation among patients infected with the same virus are unknown but stem from a complex system of virus-host interactions. Dengue fever becomes more virulent during a second infection by means of antibody dependent enhancement. After the first infection, macrophages display antibodies on their cell membranes specific to the dengue virus. By attaching to these antibodies, dengue viruses from a second infection are better able to infect the macrophages, thus reducing the immune system's ability to fight off infection.

Diagnosis

Definitive diagnosis is usually made at a reference laboratory with advanced biocontainment capabilities. The findings of laboratory investigation vary somewhat between the viruses but in general there is a decrease in the total white cell count (particularly the lymphocytes), a decrease in the platelet count, an increase in the blood serum liver enzymes, and reduced blood clotting ability measured as an increase in both the prothrombin (PT) and activated partial thromboplastin times (PTT). The hematocrit may be elevated. The serum urea and creatine may be raised but this is dependent on the hydration status of the patient. The bleeding time tends to be prolonged.

Prevention

With the exception of Yellow fever vaccine neither vaccines nor experimental vaccines are readily available. Prophylactic (preventive) ribavirin may be effective for some bunyavirus and arenavirus infections (again, available only as IND).

VHF isolation guidelines dictate that all VHF patients (with the exception of dengue patients) should be cared for using strict contact precautions, including hand hygiene, double gloves, gowns, shoe and leg coverings, and faceshield or goggles. Lassa, CCHF, Ebola, and Marburg viruses may be particularly prone to nosocomial (hospital-based) spread. Airborne precautions should be utilized including, at a minimum, a fit-tested, HEPA filter-equipped respirator (such as an N-95 mask), a battery-powered, air-purifying respirator, or a positive pressure supplied air respirator to be worn by personnel coming within 1,8 meter (six feet) of a VHF patient. Multiple patients should be cohorted (sequestered) to a separate building or a ward with an isolated air-handling system. Environmental decontamination is typically accomplished with hypochlorite (e.g. bleach) or phenolic disinfectants.[2]

Management

Medical management of VHF patients may require intensive supportive care. Antiviral therapy with intravenous ribavirin may be useful in Bunyaviridae and Arenaviridae infections (specifically Lassa fever, RVF, CCHF, and HFRS due to Old World Hantavirus infection) and can be used only under an experimental protocol as investigational new drug (IND) approved by the U.S. Food and Drug Administration (FDA). Interferon may be effective in Argentine or Bolivian hemorrhagic fevers (also available only as IND).

Epidemiology

- Cocoliztli in Mexico 1545.[3][4][5][6][7]
- The Great Yellow Fever Epidemic of 1793 in Philadelphia, PA USA. Nearly 10% of the population of 50,000 succumbed to the disease.
- Mékambo in Gabon is the site of several outbreaks of Ebola virus disease.
- Orientale Province, Democratic Republic of the Congo villages of Durba and Watsa were the epicenter of the 1998–2000 outbreak of Marburg virus disease.
- Uíge Province in Angola was the site of another outbreak of Marburg virus disease in 2005, the largest one to date of this disease.[8]
- A VHF outbreak in the village of Mweka, Democratic Republic of the Congo (DRC) that started in August 2007, and that has killed 103 people (100 adults and three children), has been shown to be caused (at least partially) by Ebola virus.
- A viral hemorrhagic fever is a possible cause of the Plague of Athens during the Peloponnesian War.[9]
- A viral hemorrhagic fever is an alternate theory of the cause of the Black Death and the Plague of Justinian[10]
- The initial, and currently only, outbreak of Lujo virus in September–October 2008 left 4/5 patients dead.[11]
- The ongoing 2014 West Africa Ebola outbreak, with record numbers already reached.

Biowarfare potential

The VHF viruses are spread in a variety of ways. Some may be transmitted to humans through a respiratory route. Although evidence for a history of "weaponization" (development into a biological weapon) does not exist for many of these viruses, all are considered by military medical planners to have a potential for aerosol dissemination, weaponization, or likelihood for confusion with similar agents that might be weaponized.[12][13]

See also

- Dr. Matthew Lukwiya (1957–2000)
- C. J. Peters

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External links

- "Viral Haemorrhagic Fever". *The National Archives of United Kingdom*. Public Health England (PHE).
- "Viral Haemorrhagic Fevers". *World Health Organization (WHO)*. United Nations (UN).
- "Viral Hemorrhagic Fevers (VHFs) Virus Families". *National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)*. U.S. Centers for Disease Control and Prevention (CDC).