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VIRAL HEMORRHAGIC FEVERS – A RECURRENT PUBLIC HEALTH THREAT

WIRUSOWE GORĄCZKI KRWOTOCZNE – POWRACAJĄCE ZAGROŻENIE ZDROWIA PUBLICZNEGO

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Wkład autorów:
A. Study design/planning
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B. Data collection/entry
zebranie danych
C. Data analysis/statistics
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D. Data interpretation
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Summary

Viral hemorrhagic fevers (VHFs) caused by viruses are severe infectious diseases that lead to serious disturbances of the body's homeostasis, in most cases accompanied by symptoms of hemorrhagic diathesis. They are spread by infection vectors such as insects (mosquitoes, ticks), airborne droplets or direct contact with contaminated material (blood, sweat, excrement, feces). There are four major groups of RNA viruses that cause hemorrhagic fevers – these include pathogens from the families *Flaviviridae, Bunyaviridae, Arenaviridae* and *Filoviridae*. Despite their common name, VHFs are distinct disease entities with different etiologies, clinical manifestations and routes of transmission. Although they have been known for several decades and are associated with illnesses in tropical countries, the risk of their occurrence, in times of globalization and widespread international travel, is increasingly high. It is not insignificant that progressive climate change is making vectors of VHFs, which years ago were seen only in tropical countries, increasingly common on the European continent and even in eastern European countries.

Keywords: recurrent diseases, hemorrhagic fevers, viruses, public health

Streszczenie

Gorączki krwotoczne wywoływane przez wirusy należą do ciężkich chorób zakaźnych, które prowadzą do poważnych zaburzeń homeostazy organizmu, gdzie w większości przypadków towarzyszą objawy skazy krwotocznej. Są rozprzestrzeniane przez tak zwane wektory zakażenia, do których należą: owady (komary, kleszcze), droga kropelkowa lub bezpośrednia styczność ze skażonym materiałem (krwią, potem, wydalinami, odchodami). Wyróżnia się cztery najważniejsze grupy wirusów RNA wywołujących gorączki krwotoczne – należą do nich patogeny z rodziny *Flaviviridae, Bunyaviridae, Arenaviridae* oraz *Filoviridae*. Gorączki krwotoczne, mimo wspólnej nazwy, stanowią odrębne jednostki chorobowe o zróżnicowanej etiologii, objawach klinicznych oraz różnych drogach transmisji. Pomimo, że znane są od kilkudziesięciu lat i kojarzone są jedynie z zachorowaniami w krajach tropikalnych, to ryzyko ich wystąpienia, w czasach globalizacji i powszechnych podróży międzynarodowych, jest coraz wyższe. Nie bez znaczenia jest fakt, że postępujące zmiany klimatyczne sprawiają, że wektory gorączek krwotocznych, obserwowane przed laty wyłącznie w krajach tropikalnych, stają się coraz bardziej powszechne na kontynencie europejskim, a nawet w krajach Europy wschodniej.

Słowa kluczowe: powracające choroby, gorączki krwotoczne, wirusy, zdrowie publiczne

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Introduction

Hemorrhagic fevers caused by viruses are severe infectious diseases that lead to serious disturbances of the body's homeostasis, in most cases accompanied by symptoms of hemorrhagic diathesis. They are spread by infection vectors, which include: insects (mosquitoes, ticks), airborne droplets or direct contact with contaminated material (blood, sweat, excrement, feces). There are four major groups of RNA viruses that cause viral hemorrhagic fevers (VHFs) which include pathogens from the families *Flaviviridae, Bunyaviridae, Arenaviridae* and *Filoviridae* [1].

Humans are the usual reservoir of viruses with regard to dengue hemorrhagic fever and yellow fever in the urban form. Other fevers caused by viruses belong to zoonoses, where the infectious agent develops and multiplies in wildlife (monkeys, birds, ticks) and domestic animals (cattle, sheep). VHFs (such as Marburg, Ebola, Lassa or Bolivian hemorrhagic fever) can spread directly between people via airborne contact or through contact with contaminated material. In other types of VHFs, the affected individual does not infect the surrounding environment [2]. It should be noted that infection with VHF can occur in the laboratory or on the premises of hospital units where medical staff come into contact with blood (infected material), insofar as the viruses present in the samples to be tested remain active [3].

Aim of the study

Viral hemorrhagic fevers, despite the common name associated with their clinical manifestations, are an extremely diverse group of independent disease entities. The aim of this study is to present the characteristics of each of them, showing commonalities and differences. Given the complexity of the problem, this study proposes a characterization of VHFs based on the routes of transmission and the possible absence or presence of vectors. Such systematization, in the authors' opinion, will allow the reader to understand the complexity of the issues described much better.

Historical overview

Viral hemorrhagic fevers emerged last century in the medical literature, with hantavirus hemorrhagic fevers described in 1951, Marburg hemorrhagic fever in 1967 and Ebola in 1978 [4]. The VHFs described in the literature were not necessarily the first infections of this kind to affect humans. For years, Song-go hemorrhagic fever with renal syndrome, caused by *Hantaan* viruses, occurred in Manchuria and eastern China [5]. The highest incidence of VHFs is reported in South-East Asia (dengue fever, Crimean-Congo hemorrhagic fever), South America (yellow fever, Lassa fever) and African areas (yellow fever, Lassa fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Ebola fever). In general, the incidence of VHFs in Europe and North America is close to zero. If recorded, it is only when the disease has been brought into the country by people returning from endemic areas or who have had contact with sick people or contaminated material [6]. To date, no native cases of known VHFs have been registered in Poland, but there is a risk of their introduction into the country.

Classification of hemorrhagic fevers

Viral hemorrhagic fevers can be classified according to the mode of transmission of the virus: by infection vectors (various types of insects: ticks, mosquitoes, rodents). These include yellow fever, dengue fever, West Nile fever, Omsk hemorrhagic fever and Kyasanur Forest Disease; by infection vectors and by airborne droplets as well as by direct contact with contaminated material. Prominent among them are Crimean-Congo hemorrhagic fever and Rift Valley fever; by the airborne droplet route or by direct contact with contaminated material. Within this group, hantavirus infections are characterized for example, Hemorrhagic fever with Respiratory Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS). The second group consists of New World hemorrhagic fevers, such as Argentine hemorrhagic fever caused by *Junin* virus, Bolivian hemorrhagic fever caused by *Machupo* virus, Brazilian hemorrhagic fever caused by *Sabia* virus, Venezuelan hemorrhagic fever caused by *Guanarito* virus; and the best known and described: Lassa fever, Marburg fever and Ebola fever.

Diagnosis of infections

The clinical features of VHFs do not allow firm conclusions to be drawn as to the nature of the etiological agent. Therefore, geographical knowledge related to the occurrence is essential. Knowledge of the distribution

of severe infectious diseases helps to provide an initial estimate of the likelihood of a particular type of disease, based on information about the country of residence of an infected individual or an individual in contact with an infected person. When interviewing a patient with symptoms of VHF, the doctor must first ask the patient about the patient's whereabouts over the past four weeks (whether they have travelled abroad) and about potential contact with people who have returned home from distant destinations [3]. For the diagnosis of VHFs, laboratory diagnosis is also used (in addition to the medical interview with the patient and the clinical picture), where the pathogen is isolated from the blood of the infected person either by molecular biology methods or by determination of characteristic antibodies with the immunoenzymatic method (ELISA test) [2]. In distinguishing hemorrhagic fevers of viral origin, the following should be taken into account: malaria, tularemia, Q fever, disseminated intravascular coagulation of different etiology, meningococcemia, typhoid fever, leptospirosis, hemolytic uremic syndrome in patients with symptoms of renal failure and hemorrhagic diathesis, septicemic Plague, hemorrhagic diathesis with thrombocytopenia, as well as *Salmonella* and *Shigella* infections in patients with fever and bloody diarrhea [2,6].

Pathogenesis of hemorrhagic fevers

The incubation period of VHFs varies from 3 to 21 days (average is 7 days). The initial phase of the disease is rapid: there is a high fever (up to 41°C) that lasts days, headache and muscle aches, chills, sometimes accompanied by coughing and/or abdominal pain, and nausea. Reddening of the skin, petechiae and swelling may also occur. In the next phase of the disease there is a slight decrease in fever, and an increase in the symptoms of hemorrhagic diathesis (intensive bleeding from various organs and systems due to damage and reduced permeability of the walls of blood vessels). With hemorrhagic diathesis, in the last stage of the disease, the following symptoms can be observed: renal and hepatic failure, abnormalities in water-electrolyte balance, reduced blood pressure, circulatory disorders and neurological disorders, including shock. The more damage of the organ structures the more their function is impaired which creates a greater risk of disseminated intravascular coagulation. Bleeding into the skin, mucous membranes, conjunctiva and, in difficult cases, even into body cavities has been observed in clinical pictures. The successful prognosis of VHFs depends on the site and severity of the hemorrhagic diathesis, the presence of systemic and organ disorders and pre-existing morbidities [2]. VHFs penetrate endothelial cells, where they replicate vigorously. The symptoms that accompany the proliferation of viral cells result from the release of specific mediators of the inflammatory process (mainly monocytes and macrophages) by previously infected cells. This leads to clotting disorders and vascular dysfunction (which are not initially the cause of extravasation). The severe phase of viral disease is characterized by the activation of biological substances such as cytokines. This causes a decrease in the permeability of blood vessels which comprises the pathogenetic starting point for the symptomatology of viral hemorrhagic fevers. The human immune system response is delayed and incapable of responding to the intense multiplication of hemorrhagic fever virus in the body. Vascular dysfunction, coagulation abnormalities, increased inflammation and intensification of necrotic processes become the cause of multi-organ failure [6].

Treatment of hemorrhagic fevers

In the hospital setting, VHFs are treated symptomatically, focusing on fluid control and replenishment and balancing water and electrolytes. Treatment of life-threatening complication and also shock management also occurs. If intravascular coagulation syndrome occurs, it is recommended that the patient be given heparin derivatives. Intramuscular infusions and the use of anticoagulants (acetylsalicylic acid derivatives), which impair platelet function, should be avoided. Antiviral treatment is difficult and reduced to appropriate oral or intravenous administration of ribavirin, which inhibits viral multiplication. With ribavirin, side effects such as reversible anemia and hyperbilirubinemia, acute pancreatitis, hemolysis, as well as bone marrow suppression and hyperuricemia are possible [2]. People with VHFs should be isolated from their environment and housed in rooms that have adequate air circulation systems. In addition, patients exhibiting coughing, vomiting, diarrhea or hemorrhagic diathesis should be placed in isolation rooms under negative pressure [6]. People in contact with infected individuals should be quarantined [2].

Infection prevention

In order to reduce the risk of contracting VHFs in endemic areas, it is essential to initiate educational activities for indigenous peoples to minimize their contact with fauna (monkeys, birds, insects and rodents),

which constitute the vector of infection. The places where people are sick should be isolated and adequately protected in order to reduce the number of new cases [6]. Preventive measures also include the use of physical protective materials (such as mosquito nets, repellents or nets in room windows) [2]. In epidemic areas, the majority of patients and victims are medical personnel, so they should meticulously follow strict standard practices when a patient is diagnosed. Only a limited number of doctors and nurses should take care of these patients with extreme caution and all healthcare personnel should use standard virus protection in the form of disposable gloves, goggles with shields, surgical masks (or with HEPA filters if in contact with the excretions of a sick person), and full-body protective suits. Protective equipment should be removed before exiting isolated rooms [6]. Single-use equipment should be properly secured and disposed of, while reusable equipment should be thoroughly disinfected [2]. In order to avoid the introduction of VHFs from endemic areas to countries where no indigenous cases of VHFs have been found, persons travelling to areas of severe infectious diseases (yellow fever regions) are obliged to receive a vaccine against the disease [2].

Viral hemorrhagic fevers which are transmitted by infectious vectors

Yellow fever

Characteristics and occurrence

Yellow fever belongs to a group of infectious diseases caused by a virus from the family *Flaviviridae.* It is found in sub-Saharan Africa and South America, mainly in the tropics or subtropics. In recent years, yellow fever has been found in Brazil, Argentina and Venezuela [7-9].

Two forms of yellow fever have been identified: the urban form (the virus reservoir is a human and is transmitted by the *Aedes aegypti* mosquito, which is the vector of infection), and the jungle form (common – where animals are the reservoir of the pathogens and the vectors of infection are mosquitoes from the family *Haemagogus, Sabathes* and *Aedes*) [2].

The incidence of yellow fever increases during the summer, when mosquitoes are most active. The yellow fever virus penetrates the lymph nodes, where it quickly begins to multiply. Then the viremia phase begins, in which the virus infects other lymph nodes, the spleen, then the bone marrow, and finally the internal organs: the lungs, liver and adrenal glands. In infected basic structural and functional components of the liver (hepatocytes) and hepatic reticuloendothelial cells (Kupffer cells), the necrotic process progresses in a pattern of apoptosis [10]. There is an increased risk of disseminated intravascular coagulation (DIC). As a result of impaired synthesis of clotting factors, thrombocytopenia and platelet dysfunction, blood extravasations can be observed, myocarditis has also been reported [3].

Clinical symptoms

Yellow fever develops asymptomatically in most cases, with occasional instances where symptoms resemble the flu. The acute course of the disease is characterized by the occurrence of VHF with an approximate 50% mortality rate. The incubation period of the disease varies from 3 to 6 days. This is followed by fever, which increases steadily, headaches and muscle aches, and may also cause reddening of the skin and petechiae [3]. In severe cases of yellow fever, three main periods of illness are observed: general symptoms are present at the beginning, then there is an unexplained recovery (within 1-2 days after the first symptoms appear), where the person's temperature stabilizes to a normal level. In the latter stages, fever rises rapidly, jaundice occurs and, in severe cases, hemorrhagic diathesis, impaired kidney function and even uremic coma can occur. If vomiting blood or disseminated intravascular coagulation occurs, the prognosis is poor (usually ending in the death of the affected person around day 4-9 of the disease). In cases of mild infection, symptoms resolve in about a week. It is worth noting that after experiencing yellow fever, the body becomes immune to the disease [2].

Based on the clinical picture, yellow fever is diagnosed, but cases with few symptoms may remain unidentified. Positive serological reactions and isolation of the pathogen from the patient's blood are crucial in making the diagnosis. Laboratory results show leukopenia, increased bilirubin and transaminase levels in the blood, and prolonged clotting and prothrombin time [11]. Recovery takes place in the form of hospitalization and is limited to the treatment of existing symptoms and, in acute cases, to the multifaceted treatment of complications [2].

Prevention

Prophylaxis includes vaccination against yellow fever, which is a compulsory vaccination recorded in the International Certificate of Vaccination or Prophylaxis. The obligation to present this is a prerequisite for crossing the border in many countries where the disease is endemic. A single dose provides immunity for 10 years. In yellow fever areas, it is also important to use physical protection in the form of appropriate clothing at certain times (dusk to dawn), mosquito nets, repellents and nets in the windows of buildings [11].

Dengue fever

Characteristics and occurrence

Among the most common VHFs is dengue fever. It is an infectious disease caused by dengue virus of the family *Flaviviridae.* Four serotypes of the pathogen can be distinguished, which is later decisive for the course of the disease. Hemorrhagic diathesis is only caused by serological types 3 and 4 of the virus. Humans are the dengue virus reservoir and it is transmitted by mosquitoes from the genus *Aedes aegypti*. There has been no reported cases of the virus being transmitted directly between humans. The involvement of an infection vector is necessary for the transmission of the dengue pathogen to occur [2]. Its distribution range includes the tropical belt and subtropical regions around the world, mainly in south-eastern areas of Asia and the islands of Oceania [12,13]. It should be noted that at higher altitudes (above 1000 m above sea level), there is a lower risk of contracting dengue hemorrhagic fever. Infections are reported during the months of May to November; however, the highest number occur during the summer from June to August [3].

Clinical symptoms

The incubation period of the disease lasts from 3 days to two weeks (in cases where there are no complications, an average of 3-7 days) [2]. To date, the incubation time for hemorrhagic fever which may occur during the illness is unknown. Dengue is mainly seen in urban areas and is particularly common in children under 14 years (80% of cases are asymptomatic). It is more severe in adults, with more severe general symptoms such as hepatomegaly, lymphadenopathy, abdominal pain and muscle complaints, anxiety and often depression. It is also accompanied by thrombocytopenia, leukopenia with lymphocytosis and decreased immunity. Immune system dysfunction is often associated with the occurrence of bacterial superinfections and activation of viruses, especially herpes type 6. In pregnant women, dengue virus causes infection of the fetus and is the cause of congenital dengue [3]. In cases with less specific symptoms, isolation of the pathogen and an observed increase in specific antibody titers are crucial. Laboratory tests, in addition to thrombocytopenia and leukopenia, show hypoalbuminemia (with the onset of hemorrhagic fever), prolongation of the prothrombin time, and increased blood urea and transaminase levels, whereas coagulation factor II, V, VI, IX and XI levels decrease [2].

Three main clinical forms of dengue have been distinguished:

- severe fever (usually accompanied by a maculopapular rash and upper respiratory tract infection);
- Dengue fever (in its first phase high temperature, headache, bone pain, joint pain and enlarged lymph nodes appear. After 2-4 days there is a drop in temperature and within several dozen hours, remission of the symptoms of the disease. The second phase of the fever, which lasts from 1 to 2 days, is characterized by the appearance of a maculopapular rash that first affects the arms and legs, then the trunk, and in a few cases the face. After the rash disappears, discoloration of the skin appears, or the epidermis begins to peel);
- Dengue hemorrhagic fever (initial symptoms are accompanied by vomiting. After 2-3 days abdominal pain, hepatomegaly, symptoms of hemorrhagic diathesis with petechiae on the face, limbs and lumbosacral region become apparent. Coma may occur. Around day 4-5 of infection, bleeding into body cavities occurs. Without appropriate treatment, death occurs 4 to 6 hours after the onset of shock symptoms [14].

Hemorrhagic fever with shock syndrome (DSS – Dengue Shock Syndrome) may occur if the patient has a history of dengue caused by another type of pathogen (particularly the DEN-2 virus), presumably an immunological reinfection [15]. An important role is attributed to circulating immunoglobulins. When their concentration is lower compared to that necessary to neutralize the disease (approximately 3-4 years after the first infection), the virus-antibody structure binds to the Fc receptor at the cell plane, facilitating the penetration of the pathogen into the endothelium and hepatocytes, where virus replication occurs immediately. High levels of the pathogen, particularly in immune complexes, are recorded in the serum of individuals who have developed hemorrhagic

fever (after the temperature decreased) [16]. Patients who did not develop hemorrhagic fever showed low levels of viremia once their temperature had decreased. Memory T cells may be crucial, as they would presumably trigger an intense release of cytokines upon repeated contact with the antigen [17]. It is possible that the effect of cytokines is to increase fibrinolytic activity, although opinions are divided on this [18]. There are two hypotheses on the pattern of endothelial cell damage by dengue virus: the first refers to a cytotoxic effect of the pathogen, the second to a cross-reaction between immunoglobulins against the microorganism and endothelial cells [19]. The consolidation of antibodies by endothelial cells has been shown to give rise to its apoptosis. In addition, there are increasing reports of antibodies (produced during infection) binding to the extracellular matrix and platelet antigens [3].

Treatment and prevention

Treatment of the initial cause of infection does not exist [3]. This is limited to preventing the occurrence of hemorrhagic diathesis and hypovolemic shock [2].

Countermeasures against the disease include the use of various types of physical protection in the form of nets/mosquito nets/repellents in windows, and wearing clothing with long sleeves and trouser legs (especially at night) [2].

West Nile Fever

Characteristics and occurrence

West Nile Fever is caused by a virus of the family *Flaviviridae*, which is part of the Japanese encephalitis antigenic complex. The virus reservoir is birds, whereas it is transmitted by the mosquitoes *Culex univitatus*, *Culex pipiens* and *Culex tarsalis*. The disease affects countries in the Nile basin (Egypt, Uganda), the territory of Israel in the Middle East (epidemic in 2000), the area of Romania and Russia in Eastern Europe (epidemics in 1996 and 1999), and areas of Western Asia. At the turn of the 21st century, numerous cases of acute West Nile fever were reported in the United States. Suspicions fell on Israel, from where the virus was probably imported. Since then, infectious disease in the form of VHFs has been a fairly serious health problem in North America [2,20]. In 2019, a total of 443 infections were reported in eleven European Union countries [11].

Clinical symptoms

The incubation period of the disease varies from 3 days to 2 weeks (3-5 days on average). In almost 80% of cases, in areas where the disease is endemic, the course of the disease is weak or asymptomatic. The remaining 20% of infections are characterized by a mild fever (very similar in its course to dengue, which lasts 3-6 days) and common symptoms such as headache, muscle aches, a feeling of weakness and fatigue, rashes on the arms and trunk, lymphadenopathy, and sometimes nausea and vomiting. In the classic course of the infection, complications are not very frequent, but if they do occur, it is especially in the elderly and immunocompromised patients. Of the group of patients, 1% undergo acute West Nile virus infection, accompanied primarily by encephalitis and/or meningitis. With such complications, high fever, headaches, disorientation, convulsions, as well as coma and paresis, among others, can occur. About 20% of those infected with encephalitis die. In young people who have not previously had the disease, mono-paresis (flaccid paralysis) may appear early in the course of the disease [21]. The diagnosis is made after interviewing the patient (whether he or she has been in regions where infectious disease is endemic) and based on the clinical picture. On the basis of tests carried out in laboratory facilities, the presence of antibodies is established (MAC-ELISA test) in the serum of the patient approximately 8 days after infection. In addition, lymphoid pleocytosis is detected after CSF analysis [2].

Treatment and prevention

The infection is treated symptomatically and for acute reinfection, targeted pharmacotherapy is used [2]. Prevention includes securing windows indoors with mosquito nets and nets and wearing appropriate clothing from dusk to dawn (long-sleeved and long-legged clothing) [2].

Omsk hemorrhagic fever

Characteristics and occurrence

Omsk hemorrhagic fever belongs to a group of infectious diseases caused by a virus from the family *Flaviviridae.* Rodents are the host of the pathogen, and the virus itself is transmitted by the ticks *Ixodes persulcatus*, *Dermacentor pictus* and *Dermacentor marginatus* [2]. It is mainly found in Siberia, but also in India and southwest Asian areas [22,23].

The incubation period of the disease is 3-8 days. Infection is usually biphasic: Phase I includes the sudden onset of fever, headache, abdominal pain and enlarged lymph nodes, and Phase II symptoms of hemorrhagic diathesis are present, with bronchopneumonia being very common [24].

Treatment and prevention

Diagnosis, treatment and prevention measures are similar to the management of yellow fever, dengue fever and West Nile fever. It should be noted that an important preventive measure is to receive the tick-borne encephalitis vaccine, which essentially provides cross-protection against Omsk hemorrhagic fever virus infection [25].

Kyasanur forest disease

Characteristics and occurrence

This is a severe infectious disease caused by a virus from the *Flaviviridae* family. The pathogen was first isolated from an infected monkey in the Kyasanur forest, hence the name of the disease. The virus reservoir is mainly monkeys and small rodents, while the vector of infection is a tick from the *Haemaphysalis* family. Infection can also occur through direct contact with contaminated material (diseased monkeys, carrion, infected body fluids). The area for the disease is quite limited. Infections are mainly reported in India (in the state of Karnataka) between February and June. Between 400 and 500 people contract Kyasanur forest disease annually, of whom 3-5% die [2,24,26]. The incubation period of the disease is 3 to 8 days. It begins with a high fever, as well as headaches and muscle aches. Sometimes the infection may be accompanied by dehydration (due to gastrointestinal dysfunction) and weak symptoms of haemorrhagic diathesis. A specific feature of Kyasanur forest disease is a drop in blood pressure, whereas tests carried out in the laboratory show thrombocytopenia and a drop in erythrocyte and leukocyte levels. In the monophasic disease course, which lasts 7-14 days from the appearance of the first symptoms of infection, most patients recover. In the biphasic disease course, a high temperature reappears approximately 2 weeks after infection, and symptoms of encephalitis are often present [25]. Diagnosis is based on virus isolation from the patient's blood and/or detection of specific antibodies using ELISA.

Treatment and prevention

Treatment focuses on symptomatic therapy: it concerns the replenishment of the water-electrolyte fluid balance and the treatment of complications (symptoms of hemorrhagic diathesis and encephalitis). Preventive measures include the use of appropriate clothing to provide protection from tick bites, as well as the use of repellents [2].

Viral hemorrhagic fevers transmitted by infection vectors and airborne droplets or direct contact with contaminated material

Crimean-Congo hemorrhagic fever

Characteristics and occurrence

Crimean-Congo hemorrhagic fever is caused by a virus of the family *Bunyaviridae* spread by *Hyalomma* ticks, which live on birds. By parasitizing them, they can transmit the virus directly to humans; infection can also occur via airborne droplets or contact with contaminated material (body fluids, carcasses, sick animals) [26]. It should be noted that infections can also arise in laboratory conditions, during blood tests of patients. The disease intensifies during the summer (June-August), when tick bites are most common. The slaughtering

and butchering of slaughtered animals poses a particular risk of virus transmission to humans [23]. The area where the infectious disease occurs is wide and includes Europe (Balkans), Africa (mainly central and north-eastern) and Asia (western areas of China, Pakistan, Afghanistan, Middle East) [27-29]. In Europe, human cases of infection have been reported in Albania, Armenia, Bulgaria, Kazakhstan, Kosovo, Russia, Serbia, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan. In June 2008, the first case was diagnosed in Greece, and Spain reported the first locally acquired case in August 2016. [11]. If the virus was transmitted by a tick, the incubation period varies from 4 to 12 days, while if the infection occurred through contact with contaminated material (e.g., meat, blood), it ranges from 2 days to 1 week.

Clinical symptoms

The course of the infection is usually severe. The first symptoms of Crimean-Congo hemorrhagic fever are a rapidly rising fever with chills and headache as well as muscle pain. Gastrointestinal symptoms and accompanying jaundice also increase. Dehydration and sudden weight loss are characteristic of such symptoms [2]. Hepatomegaly, lymphadenopathy, impaired consciousness and even depression may also occur. Laboratory investigations show high levels of transaminases in the patient's blood, thrombocytopenia and leukopenia. Infection is often accompanied by tachycardia. Changes appear on the skin in the form of a rash, which later develops into petechiae [10]. Severe cases are characterized by intense bleeding and/or shock. Sometimes the observed symptoms from the central nervous system do not give a successful prognosis. Mortality from Crimean-Congo hemorrhagic fever remains at up to 40% [30,31]. Diagnosis is based on isolation of the pathogen from serum and/or detection of high levels of specific antibodies characteristic of the disease [2].

Treatment and prevention

Treatment is based on symptomatic therapy: prevention of hemorrhagic diathesis, replenishment of body fluids, and prevention of shock. However, there have been attempts at antiviral treatment in the way of giving the patient ribavirin in appropriate doses [29]. Prevention of Crimean-Congo hemorrhagic fever infection is primarily concerned with the use of appropriate long-sleeved/long-legged clothing to protect against tick bites. In addition, strict sanitary rules must be observed when working with animals or their meat, and when dealing with patients suffering from hemorrhagic fever of unknown origin [31].

Rift Valley fever

Characteristics and occurrence

The virus that causes Rift Valley fever belongs to the genus *Bunyaviridae.* Its reservoir is cattle and sheep, and the vector is the tick *Aedes vexans*. People in contact with domestic animals and people handling these animals (breeders, veterinarians, butchers) are particularly at risk of infection. Transmission of the pathogen may occur by direct contact with contaminated material (meat, diseased animals and their feces) or via airborne droplets (laboratory infection) [2]. It is worth noting that the infection can be spread from endemic areas to other countries. The area in which Rift Valley fever occurs mainly covers the African continent and the neighboring Arabian Peninsula. The highest incidence of infection is recorded during the transitional period (late summer/early autumn). The population of mosquitoes that spread the virus is most numerous during the rainy season, and this is when epidemics of hemorrhagic fever are possible among humans and animals [32-34]. The incubation period is between 3 days and 1 week and a high fever persists for 3-5 days. Generally, the onset of the disease has an oligosymptomatic course. In severe cases of infection, two phases of the disease can be observed, very similar to dengue, accompanied by hemorrhagic diathesis, jaundice and visual impairment (1-10% of patients permanently lose their sight). Disturbance of body homeostasis is unexplained; vascular inflammation together with liver dysfunction are likely to be the cause [10]. The mortality rate is up to approximately 15% [31]. In the initial phase of infection, a particular serum concentration of specific IgM antibodies can be detected in 10% of patients.

Treatment and prevention

Treatment of Rift Valley Fever is centralized around symptomatic therapy. However, prophylaxis mainly concerns the use of physical protection (clothing, repellents) to reduce the risk of tick bites, and the observance of strict sanitary rules by groups at increased risk (breeders, butchers) [2].

Viral hemorrhagic fevers transmitted through airborne droplets or direct contact with contaminated material

Hantavirus infections

Characteristics and occurrence

Among hantavirus infections, which are caused by pathogens of the genus *Bunyaviridae*, there are two characteristic syndromes: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Hantavirus infections do not have a characteristic infection vector, but rodents constitute the host environment for hantaviruses. Infection occurs after inhalation of an aerosol that contains rodent feces. Hantavirus infection can also occur through direct contact with contaminated material. A sick person does not pose a threat to their environment [35,36]. Pathogenic hantaviruses are present worldwide; however, each area has distinctive species of common occurrence, with *Hantaan* virus dominating in Asia, *Puumala* virus, *Dobrava* virus in Europe, *Sin Nombre* virus in North America and *Andes* virus in South America [36]. In the European Union, in 2018, 29 countries reported 1,826 cases of hantavirus infection (0.4 cases per 100,000 population), mainly caused by *Puumala* virus (97%). Between 2014 and 2018, the overall reporting rate ranged from 0.4 to 0.8 cases per 100,000 population with no clear long-term trend. In 2018, three countries, Finland, Sweden and Germany, accounted for 81% of all reported cases, and Finland alone accounted for 55% of all cases [11]. Symptoms of hantavirus infection appear after the viremia phase – the immune system is probably responsible [37]. It is possible that infection of dendritic cells results in the activation of cytotoxic T lymphocytes affecting the infected endothelium [38]. IFN-gamma and TNF released at this time may potentially increase endothelial permeability. It is very likely that all pathogenic hantaviruses bind to Beta-3 integrin, which regulates vascular permeability [39,40]. It is possible that blocking this receptor reduces endothelial cell migration, leading to increased endothelial permeability [3].

Hemorrhagic fever with renal syndrome

Characteristics and occurrence

The hantavirus serotypes most dangerous to humans include: *Hantaan, Dobrava, Puumala* and *Seoul*. The reservoirs of the viruses are small rodents that contribute to transmission of the viruses by excreting them in urine, feces and saliva. Humans become infected through direct contact with infected material or via airborne droplets. It is very rare for the virus to spread to humans after a bite from an infected rodent. It is a highly contagious infectious disease with a morbidity of over 75% for the *Hantaan* genotype [2]. It is also the only type of viral hemorrhagic fever that occurs in Poland. By autumn 2011, 41 HFRS infections had been detected, of which one death had been reported [6].

Clinical symptoms

The incubation period varies from one to five weeks (about 14 days on average). Depending on the serotype, the course of the infection varies, a very severe infection, with hemorrhagic diathesis, jaundice, renal dysfunction is caused by *Hantaan* virus, the mildest – by *Puumala* virus (where mortality is less than 1%). The phases of the course of infection in hemorrhagic fever with renal syndrome have been detailed:

- phase I invasive (febrile) is characterized by a sudden rise in body temperature (even above 40°C). This may be accompanied by chills, headaches, muscle aches, abdominal pains, general weakness, pharyngitis, redness on the face and neck (sunburn-like). Vomiting and diarrhea occur occasionally and are not typical symptoms of the fever. At a later stage, bradycardia occurs. Swelling of the eyelids is also specific; subconjunctival hemorrhages may occur up to 5 days after infection. Lymphadenopathy and splenomegaly can be observed. Laboratory tests show proteinuria, hematuria, leukopenia (which may develop into hyperleukocytosis) and thrombocytopenia. Blood pressure is normal during the first phase of infection. Around day 4-5 the temperature starts to stabilize. There is a deceivingly apparent improvement in the patient's condition;
- shock stage II (hypotensive) occurs when there is a drop in blood pressure (may be rapid, uncontrollable and cause fainting, shock, and in some cases may lead to sudden cardiac arrest). The patient's condition deteriorates, and symptoms of hemorrhagic diathesis appear. This may be accompanied by swelling of

the brain (due to bleeding into the central nervous system), loss of consciousness, convulsions as well as coma. Tachycardia and hypovolemia are observed. Around day 4-9, symptoms of severe renal failure begin to manifest;
- stage III oliguria (oliguric) begins while the second phase of infection is still in progress. It lasts from 3 to 7 days. Blood pressure slowly stabilizes, while symptoms of overhydration with accompanying hypertension and water-electrolyte deficiencies start to appear. Metabolic acidosis occasionally occurs. As the disease develops, hemorrhagic diathesis progresses, and in severe cases swelling of the brain and lungs ensues. The mortality rate at this phase of infection is 50%;
- stage IV polyuria (diuresis) occurs between days 10 and 13 of the disease, the amount of urine excreted increases and becomes polyuric. Water and electrolyte symptoms continue to persist, and symptoms of renal failure begin to resolve approximately 21 days after infection. A distinctive feature of the diuresis phase is usually a successful prognosis as there is a slow recovery of the patient as hemorrhagic diathesis and water-electrolyte deficiencies subside;
- stage V recovery occurs when all symptoms of hemorrhagic fever with renal syndrome resolve. Recovery from infection can take up to several months [6].

It has been reported that the long-term effects of hemorrhagic fever can include damage to the pituitary gland, thyroid dysfunction and impaired normal functioning of the reproductive system (hypogonadism). Acute respiratory failure, jaundice with symptoms of cholestasis, as well as Guallain-Barré syndrome (muscle weakness, tingling sensation in certain parts of the body, which can lead to paralysis), DIC or hemophagocytic syndrome (an inflammatory process in which lymphocytes and macrophages are proliferated and activated due to increased cytokine production) may also occur [6]. Diagnosis of infection is based on analysis of the clinical picture and serological tests (ELISA) to detect specific antibodies. In cases of difficult identification, it is important to isolate the virus from the biological material collected from the patient (PCR) [41]. The greater the variety of serological tests used, the greater the chance of a precise result and accurate diagnosis.

Treatment and prevention

Treatment of haemorrhagic fever with renal syndrome is determined by the severity of the infection. It mainly focuses on symptomatic therapy and treatment of complications arising from progressive infection. Antiviral treatment takes the form of intravenous ribavirin for one week [2]. Prevention primarily involves avoiding contact with small rodents and their feces and contaminated material. It is important that sick patients are placed in isolation, people who come into contact are required to be quarantined [41]. Preventive measures also include vaccination. A neutralized vaccine called 'Hantavax' has been used in South Korea since 1991 and has shown a high level of efficacy in case-control studies. Among a group of nearly 1,900 vaccinated persons, no infection was recorded for VHF with renal syndrome, whereas as many as 20 cases of the disease were recorded in a control group of 2,000 persons. Overall, to date, research is ongoing to develop a completely effective and safe vaccine to protect against all pathogenic genotypes of the virus that cause hemorrhagic fever with renal syndrome [6].

Hantavirus pulmonary syndrome

Characteristics and occurrence

Hantavirus pulmonary syndrome is caused by hantaviruses, found mainly in North and South American countries, which include: *Sin Nombre*, *Hu39694*, *Lechiguanas*, *Andes* and *Oran*. As with hantavirus hemorrhagic fever with renal syndrome, the reservoir of the viruses are small rodents, which contribute to the transmission of the viruses by excreting them in urine, feces and saliva. Humans become infected through direct contact with infected material or via airborne droplets.

Clinical symptoms

The incubation period varies from 7 to 42 days. The onset of infection shows some common symptoms lasting 3-5 days, which are also found in HFRS, and which are later joined and exacerbated by symptoms of pulmonary lesions (dyspnea, cough, shallowing and shortening of breath), and gastrointestinal problems may also occur [2]. In the longer term, pneumonia with extensive edema develops [3]. The sudden deterioration of the patient's condition becomes the cause of acute respiratory distress syndrome (ARDS), which requires immediate treatment

in the ICU. Progressive acute respiratory failure and increasing symptoms of shock (caused by DIC) can cause death. The mortality rate from hantavirus pulmonary syndrome is 50% [42]. Diagnosis is based on serological tests (ELISA). In cases of difficult identification, it is important to isolate the virus from the biological material collected from the patient (Western blot) and to detect immunoglobulins against recombinant polypeptides and hantavirus proteins (*rapid immunoblot strip assay*) [42].

Treatment and prevention

Early treatment of acute respiratory failure, counteracting shock, but also supporting pulmonary ventilation, permanent control of blood pressure, hemoglobin saturation and replenishment of body fluids are the focus of treatment [2]. To reduce the risk of infection with hantavirus pulmonary syndrome, contact with rodents and their feces, as well as with contaminated material, should be avoided [2].

New World hemorrhagic fevers

Characteristics and occurrence

New World hemorrhagic fevers belong to a group of infectious diseases caused by *Junin*, *Machupo*, *Sabia* and *Guanarito* viruses, of the family *Arenaviridae*, located mainly in South America. The reservoir of infection is small rodents: mice from the families *Callomys* and *Zygodontomys* and *Sigmodon* rats, which excrete the viruses in their urine. Infection can occur by inhalation (through inhalation of infected dust), as well as with contaminated material or by ingestion of rodent-contaminated food. In the case of the *Machupo* virus, which causes Bolivian hemorrhagic fever, infection can be transmitted between people through contact with the infected person's blood or excretions, as well as through sexual contact [43]. The incubation period is between 1 and 2 weeks. The main cause of symptoms is macrophages, which secrete toxic cytokines that suppress the immune response. The disease is always severe and begins with a sudden increase in fever, accompanied by flu-like symptoms (headaches, muscle aches, a feeling of weakness, gastrointestinal symptoms) as well as speech disorders (dysarthria), convulsions and even coma. Hemorrhagic diathesis (caused by thrombocytopenia and platelet aggregation inhibitors circulating in the patient's body) occurs a few days after infection. Bleeding causes a drop in blood pressure that can lead to hypovolemic shock. Occasionally, with this type of VHF, encephalopathy is a possibility. In severe cases, mortality from New World hemorrhagic fevers is about 30%. In 70% of all infections with insignificant signs of hemorrhagic diathesis and neurological disturbances, the patient's condition improves after 7 days and there is a slow recovery process [3,43]. Diagnosis involves serological tests, analysis of the clinical picture, and isolation of the pathogen from the patient's biological material [43].

Treatment and prevention

Treatment is limited to symptomatic therapy. Prophylaxis, on the other hand, mainly involves avoiding contact with rodents and their excreta, and avoiding contact with contaminated material [2]. Vaccines against *Junin* virus, which cause Argentine hemorrhagic fever, are in clinical trials. Additionally, *Junin* and *Guanarito* virus (which causes Venezuelan hemorrhagic fever) are not known to be resistant to ribavirin, but its effect is unknown when treating infected humans. The *Sabia* virus (which causes Brazilian hemorrhagic fever) is susceptible to ribavirin, but only for post-exposure prophylaxis [3].

Lassa fever

Characteristics and occurrence

Lassa fever is an infectious disease caused by a virus of the genus *Arenaviridae*. The reservoir of infection is *Mastomys* rats. It is possible to spread infection directly between humans as well as by inhalation, by ingestion of rodent-contaminated food and by direct contact with contaminated material (blood, excreta). Lassa fever cases through sexual contact and breastfeeding have also been recorded. It mainly occurs in West Africa, especially in countries along the Gulf of Guinea. Approximately 1-3% of all infections are fatal [34]. In the European Union, two cases in the Netherlands were reported [11]. Lassa fever is highly contagious. The incubation period ranges from 5 days to up to 3 weeks. It begins with flu-like symptoms, and after about six days the patient's condition suddenly deteriorates: temperature rises, feeling of weakness, headaches, gastrointestinal symptoms and

inflammation of the upper respiratory tract. Blisters form in the mouth and also on the lips, which later become ulcerated. Facial swelling, conjunctival inflammation and a maculopapular rash all over the body are observed. If hemorrhagic diathesis is present, it has a rather mild course. In severe cases, hypotonia and hypovolemia occur. Oliguria may occur, which usually does not cause renal failure. Neurological disturbances in the form of convulsions, central hearing loss, alternating excessive agitation and fatigue, as well as coma are sometimes observed. Mortality from Lassa fever remains around 20% and for pregnant women is above 30% [34]. Lassa fever is diagnosed based on the clinical picture, serological tests (ELISA) and isolation of the virus from biological material (PCR) [34].

Treatment and prevention

Recovery takes place in the form of hospitalization and involves the treatment of the symptoms present. Ribavirin therapy is only successful if it is administered early to the patient at the correct dose (by day 6 of infection). Ribavirin is not recommended for use in pregnant women [2].

Marburg hemorrhagic fever

Characteristics and occurrence

Marburg hemorrhagic fever is a very dangerous viral infectious disease, caused by a virus from the family *Filoviridae*. The reservoir of infection and transmission routes have not been definitively identified. It is possible that the environment in which the pathogen lives and develops are the few species of monkeys (e.g. *Cercopithecus aethiops*), from which the disease (by direct contact) is transmitted from animal to human, whereby the infected human becomes another source of disease transmission and becomes a threat to their environment [2]. Between 1967 and 2012, 571 cases of Marburg disease were reported, including 470 deaths. During this period, outbreaks were reported mainly in the Democratic Republic of Congo, DRC, Gabon, Sudan and Uganda. Marburg virus outbreaks have occurred in recent years in the Democratic Republic of Congo, Kenya, Uganda and Angola (2005) and Uganda (2007, 2017) [11].

Clinical symptoms

The incubation period of the infection is 5 to 10 days. Initially, there are general symptoms in the form of headaches, muscle aches, a feeling of fatigue and fever. Later (about 5 days after infection), a maculopapular rash is observed on the body, accompanied by gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) and inflammation of the upper respiratory tract. Gradual weight loss, marginal exhaustion, and hepatic failure (along with jaundice), pancreatic inflammation and nervous system dysfunction are characteristic. Eventually multi-organ failure and shock occur, accompanied by symptoms of hemorrhagic diathesis. More than 50% mortality from Marburg hemorrhagic fever has been recorded [44]. Diagnosis is made based on the clinical picture, serological tests, isolation of the pathogen from the patient's blood and/or from tissue cultures during the first period of infection, as well as on searching for the virus later on (after convalescence or post-mortem if death occurs) [44].

Treatment and prevention

Treatment focuses on symptomatic therapy and treatment of complications arising from progressive infection (control of water-electrolyte and protein balance, prevention of shock and hemorrhagic diathesis, support of cardiopulmonary functions) [44].

Ebola hemorrhagic fever

Characteristics and occurrence

As with Marburg hemorrhagic fever, this is a very dangerous viral infectious disease caused by a virus from the family *Filoviridae*. The reservoir of infection and transmission routes have not been definitively identified. It is very likely that the reservoir of infection could be selected species of monkeys, from which (by direct contact) the virus can be transmitted to humans, or fruit-eating bats. The Ebola virus is also spread through airborne

droplets (in the case of nosocomial infections) or through contact with contaminated material (blood, feces, body fluids) or objects (needles, syringes, reusable medical equipment). An infected person is very dangerous to their environment, which they infect. There are four main types of the virus: *Ebola-Zaire*, *Ebola-Sudan*, *Ebola-Ivory Coast* and *Ebola-Reston*. Endemic areas are located on the African continent (Sudan, Gabon, Congo, Liberia, Uganda, Ivory Coast, Cameroon, Kenya) [3,45].

Between 1976 and 2012, 2,387 Ebola virus cases and 590 deaths were reported. In March 2014, an Ebola outbreak was reported for the first time in West Africa, in eastern Guinea, which spread to the neighboring countries of Sierra Leone and Liberia. According to the World Health Organization, 28,616 cases and 11,310 deaths were reported in three West African countries (Guinea, Liberia and Sierra Leone) between 2014 and 2016. Since 2014, four unrelated outbreaks have been reported in the Democratic Republic of Congo: two in Equateur province (2014 and 2018), one in Bas-Uele province (2017) and one large outbreak in North Kivu and Ituri provinces (2018-2019) [11].

Clinical symptoms

The incubation period lasts from 4 to 21 days (average 1-2 weeks). The course of Ebola virus infection is similar to Lassa fever: it begins with a rapid rise in temperature (above 40^{0}C) accompanied by headaches and muscle aches and inflammation of the throat and esophagus. The symptoms of hemorrhagic diathesis also begin to appear early. Dehydration, water-electrolyte and polypeptide disturbances occur rapidly, resulting in sudden weight loss and extreme exhaustion. Most infections are characterized by a maculopapular rash as well as liver failure accompanied by jaundice. If the symptoms of hemorrhagic diathesis and coma worsen, the patient's condition deteriorates. The mortality rate is very high at 53-88%. To date, it has not been explained why some people infected with the Ebola virus recover spontaneously when others die (and in a significant number of cases). It is known that the bodies of those who died from Ebola did not have time to produce an adequate immune response [45]. Diagnosis is made based on the clinical picture, serological tests, isolation of the pathogen from the patient's blood and/or from tissue cultures during the first period of infection, as well as on searching for the virus later on (after convalescence or post-mortem if death occurs) [3,46].

Treatment and prevention

Treatment is managed symptomatically and includes the same procedures as for Marburg fever. Prophylaxis, on the other hand, involves the strict isolation of those infected with the Ebola virus, and those who come into contact should be quarantined. There is no vaccine against the virus and no treatment for the initial cause of infection (no etiotropic therapy) [46].

Conclusions

Despite their common name, VHFs are distinct disease entities with different etiologies, clinical manifestations and routes of transmission. Although they have been known for several decades and are associated only with illnesses in tropical countries, the risk of their occurrence, in times of globalization and widespread international travel, is increasingly high. According to researchers from Imperial College London and Tel Aviv University, rising temperatures and altered rainfall patterns will be responsible for expanding the area of *Aedes aegypti* mosquitoes, which are responsible for spreading many dangerous diseases such as dengue and yellow fever [47]. It is estimated that climate change will accelerate mosquito infestations in parts of China, North America and Europe, including Spain, Portugal, Greece and Turkey. In view of progressive climate change, it should be borne in mind that VHFs, which years ago were seen only in tropical countries, are becoming increasingly common and pose a real threat on the European continent, and even in the countries of Eastern Europe.

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