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Zh. I. Borodina, O. Ye. Tsarenko *,
K. M. Monakhov, L. I. Bagautdinova

Federal State Educational Institution of Higher Education Izhevsk State Medical Academy of the Ministry of Health of the Russian Federation, Izhevsk, Russia

HEMORRHAGIC FEVER WITH RENAL SYNDROME: THE CHALLENGE OF OUR TIME

Abstract

We analyzed more than 30 original articles and reviews to evaluate the current state of the issues of epidemiology, treatment, and prevention of hemorrhagic fever with renal syndrome in the world. A literature search was conducted using the Cochrane Library, PubMed, eLIBRARY databases and official WHO, UR Rospotrebnadzor, Rospotrebnadzor of the Russian Federation, and Center for Disease Control and Prevention data.

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease characterized by fever, hemodynamic disorders, hemorrhagic syndrome and kidney damage in the form of acute interstitial nephritis with the development of acute kidney injury. It is caused by RNA-containing viruses of the Hantaan genus, belongs to the group of zoonotic infections, and is transmitted through the air.

The Udmurt Republic is one of the regions of the Volga Federal District endemic for HFRS. Annually, from 300 to 2,000 people get sick in the territory of the republic. HFRS affects the most able-bodied part of the population, mainly men aged 20–50. Mortality reaches 20% in certain years of observation. The doctor's lack of caution regarding HFRS (the initial period of the disease has similar symptoms with acute respiratory diseases) leads to late hospitalization of the patient, often with serious complications that are fatal.

The main diagnostic search is carried out by the general practice service of the outpatient clinic. The materials of the article can help to correctly establish a preliminary diagnosis, taking into account clinical and epidemiological data, as well as to prescribe the necessary amount of laboratory and instrumental tests to clarify the diagnosis.

Key words: *hemorrhagic fever with renal syndrome, current clinical course, gene polymorphism, pathogenesis, etiotropic treatment for HFRS, vaccination*

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HFRS — hemorrhagic fever with renal syndrome, UR — Udmurt Republic

Hemorrhagic fever with renal syndrome (HFRS) is an acute viral, natural focal disease characterized by systemic lesion of small vessels, hemorrhagic syndrome, hemodynamic disorders and kidney damage in the form of acute interstitial nephritis with the development of acute renal injury.

* Contacts: Olga Yevgenievna Tsarenko, e-mail: evgenia_tret@mail.ru
https://orcid.org/0000-0002-9739-3343

Background

For the first time, V. A. Targanskaya described the clinical signs of HFRS in humans in the scientific literature in 1935, during outbreaks in the Far East. World interest in this disease arose only during the war in Korea (1951–1954), when about 2.5 thousand troops from the UN expeditionary force stationed in the demilitarized zone of the Korean Peninsula fell ill. In 1976, H. W. Lee, P. W. Lee and K. Johnson isolated, using indirect immunofluorescence analysis, specific HFRS virus antigen in lung tissue samples from field mice (Apodemus agrarius coreae) [23] captured in an endemic zone near the Hantaan River in South Korea.

Etiology

In various countries, a number of causative agents belonging to the genus Hantavirus, which are pathogenic for humans, have been isolated and registered: Puumala, Dobrava-Belgrade, Seoul and Amur viruses [9].

The virus belongs to the Bunyaviridae family and to the independent genus Hantaan. More than 25 serologically and genetically distinct hantaviruses are known.

Epidemiology

The incidence of hantavirus infection ranges from 150,000 to 200,000 cases per year worldwide. The highest incidence rates are recorded in China — up to 50 thousand cases, in Russia — about 6 thousand cases per year, and in Korea — 1–2 thousand cases per year [1]. Isolated cases have been reported in Germany, Great Britain, France, Belgium, Pakistan, and Iran [2, 11]. Natural foci of infection in Eurasia are constantly expanding; cases of HFRS in the Balkans, Malaysia, and Japan have been confirmed [15]. In the European part of Russia, 98% of cases of HFRS are recorded, in the Far East — 2% of cases. Natural foci of HFRS in Russia are the Middle Urals, Cis-Urals, Ulyanovsk, Samara, Orenburg regions, and Khabarovsk Territory [3].

In the Volga Federal District, 85.5% of all cases of HFRS in the Russian Federation are registered. The Udmurt Republic (UR) is in the first place among the subjects of the Russian Federation in the incidence of HFRS and is one of the largest natural foci. HFRS affects the most able-bodied part of the population, mainly men aged 20–50. The peak incidence is in the age group of 20–29 years. Mortality reaches 20%.

The natural susceptibility to infection is high, depending on the nature of employment and the extent of contact with the natural focus. An analysis of the causes and conditions of infecting within UR indicates that in 42% of cases, infection occurred in everyday life, in 32% of cases when working in a garden, and in 16% of cases when visiting a forest. The proportion of industrial infection was 5.1%. Employments of the risk group are: chauffeurs, geologists, oil workers, builders, road workers, and machine operators.

One of the promising areas is the molecular genetic analysis of gene polymorphism in patients with HFRS [17]. Molecular genetic methods make it possible to study the heterogeneity of hantavirus populations in nature, characterize the epidemic significance of strains, and determine the quantitative load of the virus.

Hantavirus infection is a natural focal zoonosis, and the mouse-like rodents are the reservoir and source of infection for humans. A portal of entry is the mucous membrane of the respiratory tract, less often the skin and the mucous membrane of the digestive system. Infection is transmitted predominantly through air (90% of cases) (with aspiration of the virus from dried rodent feces), rarely by contact (through damaged skin and mucous membranes), and by the alimentary route (ingestion of contaminated products). Human-to-human transmission of the virus is not possible.

An increase in the incidence is observed from May to December (the infection has summer-autumn seasonal prevalence), which is associated with an increase in the number of rodents by the end of summer. The peak falls on August.

According to the State report "On the State of the Sanitary-Epidemiological Well-Being of the Population of the Moscow Region in 2018" for the last 5 years (2014–2018), 106 people fell ill with HFRS (in 2018 — 11 people).

Pathogenesis and Clinic

The first researchers of HFRS, A. I. Churilov (1941), A. I. Kazbintsev (1944), A. A. Smorodintsev (1944), and V. G. Chudakov (1957), were also the first to suggest vasotropic properties of the HFRS virus.

To date, there is no doubt the pathogenesis of clinical forms of hantavirus infection is immune-mediated [1, 3, 4]. A key role passes to the immune response of a macroorganism: an increase in the level of vasomodulators, antiplatelet agents, impaired adhesive activity of the endothelium, a

change in anticoagulation potential, structural damage to the endothelium with low activity of repair processes, the development of a "cytokine storm", an increase in vascular permeability, the development of plasmorrhea (massive capillary leak), hemoconcentration and tissue hyperhydration, followed by the development of disseminated intravascular coagulation syndrome and multiple organ failure [10].

There is also a genetically determined predisposition to severe HFRS associated with gene polymorphism. One of the most accessible approaches used in molecular genetic studies of multifactorial diseases, including infectious etiology, is to study the associations of the disease with polymorphic gene loci, the protein products of which are involved in the pathogenesis of the disease. Most studies in this direction are devoted to single nucleotide polymorphism as the most common form of individual genetic variability [12].

The generalized nature of the infection involving various organs and systems in the pathological process determines the polymorphism of symptoms regardless of the causative agent (hantavirus serotype).

In the clinical pattern of the disease, 6 mains clinical pathogenetic syndromes are distinguished:

1) General symptoms of infection.
2) Hemodynamic disorders (central and microcirculatory), hypovolemia and hemodynamic stress.
3) Acute kidney injury.
4) Disseminated intravascular coagulation.
5) Abdominal (dyspeptic) syndrome.
6) Respiratory syndrome.

Standard course consists of several periods: incubation (from 7 to 45 days); febrile (from 3 to 10 days); oliguric (4–12 days); diuretic, and convalescence (from 3 weeks to 3–12 months):

1) Incubation (from 7 to 45 days).
2) Febrile phase (from 3 to 10 days). Most patients fell ill acutely. Chills, headache, pain in muscles and joints, dry mouth, thirst, sometimes slight cough, and pronounced fatigue appear. In a small proportion of patients, the appearance of pronounced signs of the disease is preceded by a prodromal phase: general malaise, fatigue, and loss of appetite. In most patients, fever reaches high numbers (up to 38–40 °C) on the first day of the disease. The duration and height of the fever are related to the severity of the disease. During the oliguric phase, the temperature decreases; sometimes it can persist at subfebrile numbers.

An intense headache combined with fever and vomiting requires differential diagnosis with meningitis.

An objective examination reveals severe hyperemia of the skin of the face, neck, upper body, associated with autonomic disorders at the level of the centers of the cervical and thoracic spinal cord. Most noticeable signs are scleral and conjunctival injection, hyperemia of the mucous membrane of the oropharynx, and the appearance of the spotted enanthema of the upper palate. Perhaps the development of hemorrhagic syndrome in the form of petechial rash on the inner surfaces of both shoulders, lateral surfaces of the trunk and on the chest (whiplash symptom), ecchymosis at the injection site, and short nosebleeds. Symptoms of endothelial damage (cuff, pinch and tourniquet signs) are determined.

Blood pressure is normal or with a tendency to hypotension, relative bradycardia is characteristic [18].

Some patients note a feeling of heaviness in the lower back. At the end of the initial phase, there is a decrease in urine output and urinary frequency.

During this phase, an increase in serum creatinine, urea, a decrease in urine specific gravity and the appearance of single fresh red blood cells and proteinuria are observed. In most patients, complete blood count is characterized by moderate leukopenia and, less commonly, mild leukocytosis and stab shift to the left, signs of hemoconcentration (RBC and hemoglobin increase) associated with plasmorrhea and hypovolemia. The pathognomonic symptom of HFRS in the early phase is thrombocytopenia, due to the damaging effect of the virus, the development of immunopathological reactions, an increase in the adhesive properties of platelets, the formation of cell aggregates with microcirculation delay in the vessels, and a violation of the rheological properties of the blood.

3) Oliguric phase (from 4 to 12 days). Body temperature drops to normal, sometimes rising again to subfebrile: the "double-humped" curve. General symptoms reach a maximum, signs of hemodynamic disorder, kidney injury, and hemorrhagic rash intensify. The most constant sign of a transition to the oliguric phase is the appearance of

lower back pain of varying intensity: from unpleasant sensations of heaviness to sharp and painful, nausea, vomiting, not associated with the ingestion of food or medicine. Many patients have abdominal epigastric or mesogastric pain. The disease can be accompanied by both the appearance of loose stool and constipation in case of intestinal paresis. In HFRS, the blood content of toxins of intestinal origin also increases (indican, ammonia, phenol, paracresol, etc.).

The entry of intestinal toxins into the systemic circulation increases with functional bowel obstruction, which develops due to wall edema and electrolyte imbalance. Intestinal paresis is accompanied by an increase in intra-abdominal pressure, which disrupts the blood circulation in the abdominal and retroperitoneal organs (kidney) and lungs.

In the oliguric phase, the liver is enlarged and painful on palpation. Nausea, vomiting and abdominal pain predict a severe course of renal failure. Frequent vomiting, hiccup, abdominal pain, phenomena of mild signs of peritoneal irritation that are not associated with the infection, absence of stool, bloating and dry, coated tongue give the impression of an acute surgical pathology.

Asthenia and adynamia increase. The face is hyperemic; with increasing renal failure, blush gives way to pallor and, mainly in severe cases of the disease, hemorrhagic signs intensify: subconjunctival hemorrhage, ecchymosis, nosebleeds and macrohematuria, hematomas at the injection sites, less often intestinal bleeding, hematemesis, and hemoptysis. Diagnosis is characterized by visual impairment (decreased visual acuity, "flying flies", cloudy vision) associated with retinal microcirculation disorder [18, 29].

At the beginning of the oliguric phase, blood pressure is within normal limits, and in severe cases hypotension develops [34].

A detailed pattern of acute kidney injury is characterized by progressive oligoanuria and uremic intoxication, water-electrolyte imbalance, and increasing metabolic acidosis.

Blood picture reveals thrombocytopenia. An increase in the level of residual nitrogen, urea, creatinine, as well as hyperkalemia, hypermagnesemia, hyponatremia, and signs of metabolic acidosis are characteristic. In the urinalysis, massive proteinuria (up to 33–66 g/l) is noted, the intensity of which changes during the day ("protein shot"), hematuria, urinary casts, epithelial cells (the so-called Dunaevsky cells). From the second half of the oliguric phase, low urine specific gravity develops.

Significant changes occur in the state of the coagulation system. Usually, hypercoagulation persists, but in severe cases, hypocoagulation develops. It is associated with the consumption of plasma coagulation factors due to the formation of microthrombi in small vessels.

4) Diuretic phase (from 13 to 21 days). Vomiting ceases, pain in the lower back and abdomen gradually disappear, sleep and appetite normalize, the daily urine output increases (up to 3–10 l), nocturia is characteristic. The duration of polyuria and isohypostenuria depending on the severity of the clinical course can range from several days to several weeks. However, the improvement development does not always run parallel to the increase in urine output. Sometimes in the early days of diuretic phase, azotemia still increases, dehydration, hyponatremia and hypokalemia may develop, hypocoagulation persists; therefore, this phase is often called the "uncertain prognosis" stage [18, 29].

Laboratory shifts consist in a certain decrease in red blood cells, hemoglobin, and an increase in platelets. Serum urea and creatinine levels gradually decrease, hypokalemia often develops. Changes in urine (Zimnitsky test) are characterized by an extremely low specific gravity, not exceeding 1,001–1,005. A small amount of protein, moderate hematuria and urine casts, sometimes leukocyturia, a small amount of epithelium cells are determined in urine sediment.

5) Convalescent phase (from 3 weeks to 3–12 months). General condition improves significantly, daily urine output restores, urea and creatinine levels normalize. In convalescents, asthenic syndrome is detected: general weakness, fatigue, decreased efficiency, and emotional lability. There is also a vegetovascular syndrome in the form of hypotension, muffled heart sounds, shortness of breath at little physical exertion, tremor of the fingers, increased sweating, and insomnia. During this phase, there may be heaviness in the lower back, sign of concussion and nocturia, isohypostenuria persists for a long time (up to 1 year or more). Secondary bacterial infection may be associated with the development of pyelonephritis, which is most often observed in patients with acute kidney injury [18].

Despite the obvious similarity of the leading symptom complex, HFRS clinical and course features associated with different hantavirus serotypes were noted. HFRS caused by the Puumala virus is characterized by a clear alternation of clinical phases and typical symptoms with recovery in most cases. At the same time, a high frequency of respiratory syndrome in the initial period of infection with subsequent progression of acute kidney injury was noted. Often there is a liver lesion manifested by hepatomegaly, jaundice and cytolysis [4, 7, 11].

HFRS caused by the Hantaan virus has been described in detail by Korean, Chinese, and Russian clinicians; it has not changed much at present [10, 13]. It is characterized by a typical cyclic course, the severity of acute kidney injury and hemorrhagic syndrome. In the Far East of Russia, severe forms of Hantaan infection account for up to 30–40% of observations in the Khabarovsk, Primorsky Territories, and the Amur Region, which makes this pathogen more virulent than Puumala virus [13].

Severe forms of HFRS associated with different hantaviruses demonstrate the entire symptom complex of multiple organ failure in the form of various combinations of hemodynamic disorders and dysfunction of the kidneys, liver, heart, lungs, and nervous system.

Typical complications of HFRS, such as pulmonary edema, rupture of a kidney capsule, intestinal and uterine bleeding, disseminated intravascular coagulation and acute kidney injury, are the causes of death.

Complications

Acute kidney injury (AKI) is a severe clinical syndrome of the acute phase of HFRS [4]. In patients with HFRS, isolated cases of chronic kidney disease (CKD) have been described, including those requiring renal replacement therapy [7, 22, 34]. However, authors from the Far East region, where the most severe cases of HFRS are observed within Russia, did not describe outcomes in chronic kidney disease [20].

The development of DIC accompanies all cases of TSS in HFRS.

As a complication of HFRS (with indicating in the diagnosis), DIC is considered for life-threatening thromboembolic (rarely: pulmonary embolism, ischemic stroke, etc.) or hemorrhagic (gastrointestinal bleeding, hemorrhagic stroke, hemothorax, etc.) manifestations [34].

Clinical signs of lung damage in hemorrhagic fever with renal syndrome (HFRS), according to several authors, are recorded in 6–18% of patients and are observed mainly in severe cases of the disease [24]. Pulmonary edema with progressive respiratory failure is one of the causes of fatal outcomes in HFRS and is a constant finding in pathological examination. At the same time, data on the features of the pulmonary pathology development in this disease remain scarce and are given only in reports regarding the clinical description of respiratory disorders in seriously ill patients.

A number of authors [21] noted a significant prevalence of lung tissue lesions in HFRS and demonstrated the pathogenetic heterogeneity of these lesions. On the one hand, there is a pulmonary pathology of the initial period in the form of respiratory distress syndrome, which is based on an increase in the permeability of the endothelium of the pulmonary vessels under the influence of the vasotropic activity of the causative agent, and on the other hand, there is nephrogenic pulmonary edema, which occurs at the peak of acute kidney injury and is a complication of HFRS.

According to published data, pulmonary damage in patients with HFRS is observed with all serotypes, however, with a different frequency. Moreover, the fact that there is no single term for the designation of pulmonary pathology in HFRS by various researchers draws attention. Pathogenetically, single clinical and radiological changes are interpreted as "respiratory syndrome" [6], "pulmonary-renal syndrome" [10], and "hantavirus pulmonary syndrome on Puumala infection" [9].

Laboratory diagnosis of the disease consists of determining antibodies to hantavirus, indicating a specific antigen and hantavirus RNA.

Disease Outcomes

Among the outcomes of acute kidney injury, the most frequent is recovery. According to the UR Rospotrebnadzor data, fatal outcome is observed in 1–3% of cases [3].

Outpatient Follow-Up

After discharge from the hospital, patients need follow-up for timely identification and treatment of the consequences of the disease. Patients are discharged after clinical and laboratory recovery, but not earlier than 14 days from the onset of the disease. Patients are discharged with open sick leave, which is extended for a period of 10 days. The duration of the release from work is determined by the severity of the disease.

Outpatient follow-up lasts from 1 to 3 months. Subsequently, check-ups should be carried out once every three months during the first year and 2 times during the second year after discharge. The first check-up is carried out in 1 month after discharge with urine, urea, creatinine and blood pressure examination, then — in 3, 6, 9, and 12 months. Subsequently, the follow-up includes: nephrologist consultation, blood pressure monitoring, fundus examination, urinalysis, and Zimnitsky test.

In the absence of complaints and internal organ changes, after this period, patients with a history of HFRS are deregistered. During the convalescent phase, the patient is advised to avoid heavy manual labor, shaking during transferring, hypothermia and overheating, visiting sauna, playing sports for 3–6–12 months, depending on the severity of the disease.

Treatment

HFRS treatment includes detoxification, antioxidant therapy, azotemia and protein catabolism management, correction of water-electrolyte imbalance and acid-base state, management of DIC, prevention and treatment of complications (cerebral edema, pulmonary edema, uremia, hemorrhage in pituitary gland and other organs, bacterial complications). The question of pathogenetic treatment and the use of drugs is debatable: ribavirin, icatibant, favipiravir, anti-hantavirus monoclonal antibodies. A number of authors noted the insufficient effectiveness of ribavirin intravenous administration in HFRS [38.59]. Drugs are being developed based on avb3 (heterodimer of transmembrane cell receptors interacting with the extracellular matrix and transmitting extracellular signals), VEGFR2 (Vascular Endothelial Growth Factor Receptor 2) and SFK (Src family kinases) inhibitors.

Prevention

A promising issue is the prevention of the disease. In anti-epizootic work, nonspecific and specific prevention is distinguished.

Nonspecific prevention includes the destruction of rodents in foci, the use of respirators when working with dusty rooms, the storage of products in warehouses protected from rodents and other constantly acting and universally implemented measures of veterinary-sanitary and organizational economics nature aimed at the prevention of infectious diseases.

Measures for the prevention of infectious diseases in the territory of the Russian Federation are regulated by the sanitary and epidemiological rules (SP 3.1.7.2614-10) of 2010: "Prevention of Hemorrhagic Fever with Renal Syndrome". The nature of specific preventive measures is determined by the characteristics of the infectious disease, the epizootic situation of the economy and the surrounding territory (region).

The most effective and reliable method of preventing HFRS is vaccination in contaminant areas. Hantavirus vaccines are currently being used in South Korea, China and Japan. Vaccines are prepared on the basis of the hantavirus serotype Hantaan, common in the Far East. RAMS Institute of Poliomyelitis and Viral Encephalitis named after M. P. Chumakov developed the first vaccine against hemorrhagic fever with renal syndrome (HFRS), "CombiHFPS-Wak", which is a bivalent, whole-virion, inactivated, concentrated, adsorbed vaccine. "CombiHFPS-Wak" contains antigens of two serotypes of the hantaviruses Puumala and Dobrava. There are currently no vaccines approved in Russia. Thus, HFRS is currently characterized by a high incidence rate with the formation of moderate and severe forms and frequent development of complications.

The effectiveness of vaccination has been confirmed over the past 20 years in China, South and North Korea. However, HFRS vaccines produced in these countries based on the Hantaan and Seoul viruses do not have a protective effect against the Puumala virus. The introduction of a cultural, bivalent, inactivated, adsorbed HFRS vaccine "CombiHFRS-Wak", which has passed preclinical tests for compliance with the requirements for immunobiological medicinal products for human use, would reduce the incidence of HFRS.

Conclusion

Hemorrhagic fever with renal syndrome is a widespread zoonotic infection, the relevance of which is determined by the increase in the incidence rate in the world with the expansion of the natural foci, a frequent severe course of the disease, and a high mortality rate among the able-bodied population. Timely diagnostic and treatment of the population is of great importance in the prevention of severe course, complications and adverse outcomes of HFRS. The main diagnostic search is carried out by the therapeutic service of the outpatient clinic.

To ensure a favorable outcome of the disease, it is necessary to correctly establish a preliminary diagnosis, taking into account clinical and epidemiological data, and also to prescribe the necessary amount of laboratory and instrumental tests to clarify the diagnosis. Conducting anti-epidemic measures, the introduction of a cultural, bivalent, inactivated, adsorbed vaccine against HFRS can help reduce the incidence.

Contribution of Authors

Bagautdinova L.I. — concept and design development
Borodina J.I. — interpretation and critical analysis of the results, formulation of conclusions
Monakhov K.M. — collection and analysis of primary clinical data
Tsarenko O.E. — manuscript writing

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