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Case Report

Facing of Family Doctor with Hantavirus Infection

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Abstract

BACKGROUND: Hantavirus infection is manifested as an urgent, severe and life-threatening disease caused by Hantavirus. The virus affects human endothelial cells. The natural reservoir of the Hantaviruses is chronically infected rodents. Human infection is accidental. Occurs by intake of contaminated food or inhalation of contaminated secretion from infected rodents' excretions have an increased risk of contamination. The most affected persons are people who work in nature. The virus causes haemorrhages, fever and acute renal failure. The disease appears more frequently in endemic regions with the lethality of 6-15%. The disease can surprise doctors with severity, urgency and undefined clinical picture. Fast clinical evaluation, proper and urgent diagnosis and treatment can improve the safe life of these patients.

CASE REPORT: We report a case of 45 -year-old male patient worked as a shepherd on mountain Babuna near the city of Veles in the Republic of Macedonia at the end of the summer in the year 2017, presented with prolonged hemorrhagic fever with renal syndrome. The clinical presentation and lab findings support the diagnosis of Hantavirus infection with acute renal failure.

CONCLUSION: It is necessary to raise the awareness of the family doctors for the hantavirus disease, especially in countries with sporadic cases, as in our country. It needs for prompt and timely diagnosis, timely hospitalisation and initiation of therapy.

Introduction

Hantavirus infections (order *Bunyavirales*, family *Hantaviridae*) attract more attention in the world. For the first time were reported entities in Korean wore, beside river Hantan. Three thousand soldiers were faced with febrile fever, acute renal failure, shook, with the lethality of 7%. The cause of the disease is *Hantavirus* – single strain RNA virus with 21species and more than 30 genotypes. *Hantavirus* affects human endothelial cells and causes vascular instability [1], [2]. The natural reservoir of the *Hantaviruses* is chronically infected rodent. Virus and the host have a long period of co-evaluation without the existing disease [3]. Infection is accidental. Infection occurs by ingestion of contaminated food with excretions (urine, faeces and sputum) or inhalation of contaminated dust from an infected rodent. People (shepherds, foresters, woods) with close contact with rodents' excretions have an increased risk of contamination. The most common types of *Hantaviruses* in Asia are Amur and Seoul virus with the lethality of 17%. Seoul *Hantavirus* (SEOV) causes mild to moderate hemorrhagic fever with renal failure in Russia, South Korea and China. Few tens to a few thousand, human infections were diagnosed in China and four sporadic human cases in the United Kingdom, France Netherlands [4] and Germany [5], [6]. Dobrava, Tula, Puumala and Saaremaa viruses are most frequent with the most severe clinical pictures on Balkan [7]. In our region, the most frequent is Dobrava *Hantavirus*. The infection from human to human is very rare, with the exception of Ande virus in South Argentina. Puumala virus stands as the main contributor to hemorrhagic fever with renal syndrome (HFRS) in Europe, while

the Dobrava virus is the causative agent of the most severe HFRS causes in central Europe. The mortality rate for Dobrava viruses is more than 10% [8]. Bruges virus is a novel *hantavirus* found harboured by the European mole (Talpa europea) which is the host of Nova virus. These findings highlight the complexity of *hantavirus* evolution and the importance of further investigation of *hantavirus* reservoir relationship [3]. There are three types of the disease with different clinical manifestations, but often some of the symptoms are found in the three types of disease, especially in the first two types: 1. NE (nephritic enteropathy), 2. HFRS (hemorrhathe gic the fever with renal syndrome), and 3. HPS (Hemorrhagic pulmonary syndrome). HFRS last from 7-36 days with the lethality of 6-15% and is the most frequent [9]. The *Hantavirus* causes systematic damages of capillaries and venules. It induces hemorrhagic manifestation and vascular disturbances, which causes acute renal failure as a result of interstitial haemorrhages and infiltrates [2]. The clinical expression of the disease is classified in 5 phases: febricity, hypotension, oliguria, diuresis and convalescence [10]. The first phase is characterised by the predominance of fever. The first 3 to 4 days are characterised by the appearance of the chest and abdominal pain, fever, myalgia, photophobia, malaise, diarrhoea, vomiting, diffuse redness on the face. Symptoms in this period are very non-specific and can be difficult to differentiate from a simple virus infection accompanied by diarrhea. In the fourth and fifth day of illness, appear diffuse petechial hemorrhages, enanthema on the hard palate, hemorrhages in conjunctives, involvement of the temporal visual field, coughing, hematuria and proteinuria.

The second phase is characterised with predomination of hypotension: The hypotension is developed in the 3-6 days of disease with strong expressed malaise, shook, leukocytosis and thrombocytopenia, with a wide range of renal impairment – (acute tubulointerstitial nephritis) or (necrotising glomerulonephritis, and IgA nephropathy). The severity of thrombocytopenia in a patient with HFRS may predict disease severity and critical patients' survival [11]. This phase is also nonspecific and difficult to recognise and reminiscent of dehydration, caused by prolonged fever and diarrhoea. The third phase is with the appearance of oliguria: In that phase, if it is not done on time a complete blood account analysis which is characterised with thrombocytopenia and increased values of blood creatinine, it is not possible to recognise the disease. If the disease is not recognized at this stage of the disease, the likelihood of a fatal event is possible due to advanced acute renal failure. The eighth day of the disease is also characterised by hemorrhagic manifestations.

The fourth phase is characterised by diuresis. If the patient survived, an intensified diuresis occurs on the eleventh day of the illness.

The fifth phase is convalescence, which lasts 2 weeks to 6 months. All five phases are not strictly delineated. Sequels are rare with chronic renal failure and hypotension. Extrarenal symptoms in this disease are presents as acute myopia, convulsions, myocarditis, gastrointestinal bleeding, liver, pancreas, thyroid gland and pulmonary damages.

The diagnosis is established based on the clinical picture and laboratory investigations. The main factor on which depends on the severity of the disease is the degree of endothelial permeability and genetic predisposition, HLA-B8, DRB1*0301, C4A*Q0, or DQ2 alleles, HLA B35. Thrombocytopenia appears at the early stage of the disease. Detection of specific IgM antibodies confirms the diagnosis [12]. Increased levels of procalcitonin could be predictive of disease severity, secondary bacterial infection and mortality in patients with HFRS caused by *Hantavirus* infection [13]. There is no applicative etiological therapy. Supportive therapy, such hemodialysis, correction of bleeding and platelets cells, blood pressure, antibiotic treatment of bacterial infection, anticoagulant therapy and supervision. Ribavirin and interferon have limited results. Prevention is particularly important. It is recommended to avoid places with an increased presence of mice or other rodents to reducing contact with contaminated excretions. Preventive measures in the houses and the environment by eliminating the food sources are useful. These measures could make home and workspaces unattractive to rodents [14]. There are needs of increased efforts for preparing effective and reliable vaccine with recombinant RNA technology. The potential effect of the inactivated *Hantavirus* vaccine remains controversial. It appears in the research in the Republic of Korea; the vaccine is moderately effective for patients (older patients) at high risk for HFRS [15] Current vaccines are ineffective, with development of neutralising antibodies [16]. Until today there is no suitable vaccine with inactivated *Hantaviruses* that will provide adequate protection in humans.

Case Report - Our Experience with Hantavirus Infected Patient - (Hemorrhagic Fever and Renal Syndrome)

The present article reports a case of 45 old male patients, presented with *Hantavirus* infection disease. He worked as a shepherd on the Babuna Mountain near Veles in the Republic of Macedonia. History is negative for any disease of interest. Epidemiological history is positive, and it is connected with eating contaminated watermelon. He visited his family doctor after 6 days of the onset of symptoms. The first symptoms were high temperature, > 38.5°C, which lasted 5-6 days, prolonged vomiting, diarrhoea for 5-6 days, dorsal, strong lumbar and sacral pain,

abdominal pain, myalgia, pronounced fatigue, reduced coordination, and cough**.** The patient's entire condition was unspecific and reminded of gastrointestinal infection and the common cold. By first physical examination in the family doctor's office was found the existence of elevated temperature > 39°C, bradycardia, diffuse redness of the face, photophobia, hypotension, petechial haemorrhages of hard palate and conjunctiva and temporally disturbed vision, reduced coordination, slow speech, hoarse voice and cough. Lab analyses were performed in the first visit of the patient. The measured blood pressure was 100/70 mmHg.

Table1: Laboratory results of the first and second day of ambulatory examinations

	Hb	Er	Le	Gr	HCT	PLT	Glycemia	Urea	Cratinine	ALT	AST
First day	195 g	7.15	11.44x10^{9}/L	83.8	69	45	6.9	11.8	159	43.5	68
Second day	195	7.26	19x10^{9}/L	85.3	70	45	8.1	17.4	374	44.5	69
Ref. values	120-174gr/l	4.00-5.50x10^{12}/l	5.00-10.00x10^{9}/ l	40-70%	36-52%	150-400x10^{9}/l	4.2-6.5 mmol/l	1.7-8.5 mmol/l	56-120 µmol/l	< 45 U/l	< 45U/l

The Laboratory results of the first ambulatory day are presented in Table 1. Blood analysis showed high values of haemoglobin, erythrocytes and hematocrit (haemoconcentration), increased number of white blood cells, low platelet counts, increased values of blood sugar, creatinine, urea and alanine transaminase (ALT), aspartate transaminase (AST) values. Urine analysis showed mild proteinuria and hematuria. We suggested urgent hospitalisation because of the complexity of the symptoms, high fever and signs of renal failure. He rejected to be hospitalised, but finally, he decided to visit as with his wife the next day. We started intravenous rehydration and symptomatic treatment.

During the review of the patient's condition, the deterioration of the health status was observed, with frequent vomiting, hypotension, oedema on the face, vision disorder, pronounced malaise, enanthema of the soft palate, conjunctivas bleeding and appearance of the oliguria. The measured blood pressure was 90/60 mmHg. The second-day lab analyses were done. Prompt worsening, with the persistence of thrombocytopenia, haemoconcentration, hyperglycemia, uremia, high levels of creatinine values, liver and pancreas damages were observed.

The patient was immediately referred to the General Hospital, Department of Internal Medicine in Veles, for further hospital treatment. Laboratory analyses, chest and abdominal x-ray were performed. An abdominal x-ray was normal, without signs of acute surgical disease. The chest x-ray was normal. Because of the appearance of strong abdominal pain, vomiting of bloody content and unclear clinical picture of the disease was made unsuccessful gastroscopy attempt in the local hospital. Shortly after that, complete anuria appeared (creatinine value 541 µmol/l, thrombocytes 29 x 10^{9}/l, leucocytes 22.5 x 10) and the patient was forwarded as an emergency patient to the University Clinic for Nephrology (UCN) Skopje where were done lab analysis and serological analysis. Serological analyses (ELISA) done at the Laboratory for Virology and molecular diagnostics, Institute of Public Health, showed the existence of IgM antibodies against *Hantavirus*.

The serological analysis was not performed again. After establishing the diagnosis and started hemodialysis patient was transferred at University Clinic for Infectious disease and febrile conditions (UCIDFC) Skopje. Consultation with Transfusion department was done twice times, where was analysed coagulation.

Table 2: The results of the blood coagulation analyses

Transfusion department	First analysis	Second analysis-after 2 days	Reference values
Number of platelets	33	96	150-450x10^{9}/l
Hematocrit	43.2%	20.5%	35-50%
Prothrombin time	11.3	12.32	9-14.2 sec.
Activated partial thromboplastin time	39.59	45.01	27.9-37.7%
Thrombin time	24.64	21.73	16.1-24.1 sec.
D-dimer	4306.42	2553.13	0-500 ng/ml

The first analysis showed consumptive thrombocytopenia with activation of secondary thrombolysis and hemolytic anaemia. The second analysis was done after started anticoagulation treatment. Hemodialysis was performed three times at UCN. The patient was hospitalised 21 days at UCIDFC, and he had important improvement of the general condition and renal function. Lab results during hospitalisation are presented in Table 3.

Table 3: Lab analyses performed at UCIDFC

Days of the hospital treatment	4-th day	6-th day	8-th day	11-day	14-th day	17-th day	20-day	21-th	Reference values
Hb	128	76	103	100	93	96	103	106	120-174 g/l
Er	4.1	2.5	3.4	3.2	3.1	3.2	3.4	3.5	4.00-.50.50x10^{12}/l
Le	25.8	20.2	19.5	15.0	10.4	5.3	7.9	8.2	5.00-10.00x10^{9}/l
PLT	46	100	90	119	150	129	99	303	150-450x10^{9}/l
Hematocrit	36	22	31	30	29	31	33	33	35-50%
Gr	74	65	77	76	69	52	58	49	40-70%
Glycemia	6.7		5.7	5.7	6.3	5.6	5.3	3.5	4.2-6.5 mmol/l
Urea	26	36.7	18.8	17.9	14.1	6.3	5.3	3.5	1.7-8.5 mmol/l
Creatinine	604	630	563	364	340	128	89	87	56-120 µg/l
ALT	27		80		95				<45 U/l
AST	35		64		69				<45 U/l
LDH	944	984	1157		958				225-450 U/l
CK	162	190	31		51				24-190 U/l
K	3.5	3.7	3.8	3.6	3.9	4.3		4.9	3.6-5.5 mmol/l
Na mmol/L	125	125	133	135	144	145		143	135-155 mmol/l
Ca mmol/L	1.71	2.3	1.98	1.92	1.95	2.17		2.39	2.02-2.60 mmol/l
ABS-pH	7.41	7.47	7.43						
Albumins			26		27				38-51 g/l
Globulins			28		31				26-46 g/l
Total proteins			54		58				66-87 g/l
urine						20-25Er,6-8 Le, the mass of bacteria		10-15Le 6-8Er	
CRP	25		33		34	19			
agriculture							Klebsiella pn.esbl+		
Serology for Hantavirus IgM Antibodies							positive		

The results are connected with the severity of clinical pictures. He received supportive therapy. Correction of bleeding and platelet was done with blood transfusions and blood products on several occasions. Rehydration with intravenous infusions, anticoagulant therapy, antibiotics treatment, hemodialysis and supervision was done. The

complete patient's treatment provided complete recovery without sequels. Control examinations were performed regularly.

Phylogenetic analysis of the *Hantavirus* was performed at the Medical School Aristotle University of Thessaloniki, conforming Dobrava serotype.

Established Diagnosis: Hemorrhagic fever with Renal Syndrome, *Hantavirus* infection (Dobrava serotype).

Discussion

Hantavirus infections with HFRS are periodically seen in our country at the end of the summer and autumn among persons who are working in nature. The diagnosis and treatment can be difficult, especially in the region where the disease is not frequent, and the doctors are not familiar with that disease. *Hantavirus* infections are more frequent in Korea and China. The minor peak season is from May to July, and the major peak is in the harvest season, from October to December when the ground is disturbed, and there was a lot of dust [17]. The disease has a high percentage of mortality. The mountain Babuna and region around cities Tetovo and Gostivar are endemic regions for *Hantavirus* infection, but the disease appears periodically. According to data of the Institute of Public Health in 2017, 17 patients with detected *Hantavirus* infection were reported, and calculation of fatality rate for this disease is 11.8%. In the 2018 year, 9 cases of *Hantavirus* infection were reported. Dobrava serotype was confirmed for the cases in 2017. Two patients died, and 3 patients had chronic kidneys failure**.** Due to the need for treatment and prevention of the disease, many studies have been undertaken, including the efforts on creating a new, more effective vaccine [18]. Despite the emergence of this disease, there is a space for improvement concerning making a rapid and accurate diagnosis and implementing appropriate care. The family doctors and clinicians are facing challenges in dialling with the unfamiliar disease in people who are working in nature. *Hantavirus* infection with HFRS is a very urgent disease with very prompt developing of the spectrum of unspecific symptoms which can make difficulties in establishing of the diagnosis, especially in regions where the disease is not very frequent, and it can cause delayed of the treatment. Every delayed of the treatment can be the reason for fatal consequences and sequels. Making algorithm is not possible because the disease is not very frequent, and clinical presentation is not specific.

The goals of the treatments are quick recognition, lab investigations, prompt symptomatic treatment, and hemodialysis in patients with anuria or oliguria. *Hantavirus* disease should be considered in the differential diagnosis of leptospirosis and rickettsiosis, unspecific gastroenterocolitis, severe atypical pneumonia, pneumonia influence, heart failure, etc. Accurate diagnosis and timely initiation of the therapy are critical to the management. The main diagnostic method is the serological analysis of elevated Ig-M antibodies for *Hantavirus* [12]. Risk factors for *Hantavirus* infection are winter temperature, population density and enough available food for rodent [19]. Preventive and education measures are crucial. Many attempts have been made to produce a vaccine for *Hantaviruses* for different types, but most often it is unsuccessful.

In conclusion, *Hantavirus* disease has an unclear and profuse clinical picture with different and variable symptoms in people who work in nature. The symptoms are prolonged febricity, lumbosacral pain, abdominal pain, vomiting, malaise, dehydration and signs of acute renal failure, thrombocytopenia, and often looks like a simple cold and gastrointestinal virus infection. It is necessary to raise the awareness of the family doctors for this disease, especially in countries with sporadic cases, as in our country. It needs for prompt and timely diagnosis, timely hospitalisation and initiation of therapy. There is not etiological therapy, but symptomatic treatment can safe a life. Using preventive measures and education can reduce the risk of infection. Eradication of environment of rodents' excretions is useful in the situation of lack of proper vaccines.

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