

## **Haemorrhagic fever with renal syndrome.**

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### **Abstract**

**We present the case of a young male diagnosed with haemorrhagic fever with renal syndrome. The patient presents himself with flu-like symptoms, with a rapid aggravation of the clinical and biological status towards a hemorrhagic syndrome and acute renal failure. Antibodies anti-Hantavirus (ELISA method), confirmed a recent infection. Hantavirus, classified in the Bunyaviridae family may cause two clinical syndromes: haemorrhagic fever with renal syndrome and pulmonary hantaviral syndrome. Wild rodents serve as agent's host.**

**Keywords:** Fever, Myalgia, Headache, Thrombocytopenia, Acute renal failure, Hantavirus.

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### **Introduction**

The diagnosis of the hemorrhagic fever with renal syndrome involves a severe prognosis depending on the involved virus, with a mortality that varies between 5-15% for Hantaan and lower than 1% for Puumala pursuant to the Centers for Disease Control and Prevention [1-6]. The disease's evolution is unpredictable, in the most cases with complete remission of the acute renal failure and the clinical symptoms but there are cases with the tendency to chronic renal disease (which can require haemodialysis or renal transplant) or death [7-10]. The evolution of the presented case was toward chronic renal disease (BRC stage III) with the nephrological observing in dynamic and the taking into consideration of a renal transplant if the disease would progress to the final stage.

### **Case Report**

The case of a 30 year old patient, who loves hiking, is presented. He has no other significant personal pathological antecedent. He presents himself at the emergency room with the following symptoms: general sickness, myalgia, frontal headache, fever, shiver, fatigue, low visual acuity that have had a progressive evolution during the last week. Therefore, the patient was hospitalized in the infectious disease section before his hospitalisation at the Internal Medicine section of the Clinical Emergency County Hospital Brasov.

From a clinical point of view, the patient does not have fever and has normal lung sounds, Blood pressure=110/70 mmHg, Heart rate=100 bpm, regulated, diffuse abdominal pain, normal intestinal movement for faeces and gas, rectal examination negative for rectal bleeding, hepatosplenomegaly, without an initial clinical hemorrhagic syndrome, present diuresis (1500

ml/24 h), hemodynamic ally balanced, without neurological symptoms and without signs of meningeal irritation.

Laboratory examinations reveal slight polyglobulia, leucocytosis with neutrofilia, severe thrombocytopenia (24.000/ul), important nitrogen retention, liver cytolysis, dyselectrolytemia with hiponatremia, hyperglycaemia. The abdominal sonography shows hepatosplenomegaly, liquid surrounding the liver, in the intestines and in the recto-urinary bladder space. The lungs and heart radiography and the cerebral Magnetic Resonance Imaging (MRI) reveal no changes.

The haematological examination and the medullar puncture describe haematological changes in an infectious context.

The quickly unfavourable biological dynamic imposes the transfer of the patient at the National Infectious Disease Institute "Prof Dr. Matei Bals" in Bucharest, suspecting a leptospirosis.

The patient has hemorrhagic syndrome (hematoma of the right shoulder, epistaxis, upper gastrointestinal bleeding, frothy hemoptisis), dyspnoea, oligoanuria, orthostatic hypotension.

Biological there is still a leucocytosis with neutrofilia, severe thrombocytopenia (6.000/ul), positive procalcitonine, hyperamilemia, hyperglycaemia, high values of the LDH, the persistence of the liver cytolysis, the nitrogen retention, the dyselectrolytemia with hyponatremia, negative cultures from the biological liquids (peritoneal, pleural, hemocultures).

The lungs and heart radiography and the chest and abdominal computerized tomography reveal bilateral pleural effusion with passive pulmonary collapse.

Taking into consideration the clinical, epidemiological and paraclinical investigations, which were conducted until this

moment, the stage diagnosis is represented by: Sepsis with a probably abdominal starting point, acute pancreatitis, polyserositis, autoimmune disease in observation, acute renal failure, and hemorrhagic syndrome through severe thrombocytopenia.

By using antibiotics with a large spectrum, human immunoglobulin's, corticoids, hydroelectrolytical and acid-base balancing fluids, diuretics, platelet transfusion, insulin, symptomatic treatment, the clinical and biological evolution of the patient was slightly favourable with the remittance of the severe thrombocytopenia and the hemorrhagic syndrome but with the persistence of the important nitrogen retention and the associated hyperpotasemia. Because of the acute renal failure, that was not responsive to the volemic refillment and the diuretics, the initialization of the hemodiafiltration was required, under which the diuresis begins once again but with the maintainment of the increased values of the nitrogen retention.

Because of the presence of the hemorrhagic syndrome, fever, polyserositis, acute renal failure, a differential diagnosis is required with: autoimmune diseases (Autoimmune Hepatitis, Systemic Lupus Erythematosus, Wegener Granulomatosis, Trombophylia, Miositis), infectious diseases (Epstein Barr, Human Immunodeficiency Syndrome, *Toxoplasma Gondii*, *Citomegalovirus*, Flu, Pneumonia with *Chlamydia Pneumoniae*, *Mycoplasma Pneumonia*, Leptospirosis, Viral Hepatitis, Tuberculosis) and hematologic diseases (Idiopathic Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura, Hematological Hypersplenism).

The lack of the etiological diagnosis imposes other biological investigations in order to acquire an immunological or infectious cause, including a serological one for the hemorrhagic fever with renal syndrome and Antibodies anti-Hanta virus IgG/IgM (ELISA method), whose serological profile was favourable for a recent infection.

The remission of the sepsis and the clinical improvement but with the persistence of the nitrogen retention requires a reorientation of the patient towards the nephrology department, where the treatment with haemodialysis is continued and the treatment with prednisone is started. During the hospitalization of the patient on the nephrology department, the haemodialysis sessions are stopped because of the tendency of the nitrogen retention values to drop. The patient remains in the nephrological monitoring program because of the persistence of the high values of the nitrogen retention.

Positive diagnosis for the presented case: Hemorrhagic fever with renal syndrome, chronic renal disease stage III ( $Cl_{creat}=30.7$  ml/min/1.73 m<sup>2</sup>) post-acute renal failure at hantavirus.

## Discussion

The infection spreads through the inhalation of aerosolized rodent excreta, the inoculation takes place either at the

conjunctival level or at a cutaneous injury (pre-existing or direct) or direct through the bite of the animal [2,11].

There are more phenotypes of the Hantavirus respectively: Hantaan, Seoul, Dobrava, Puumala, New York-1, which cause two clinical syndromes: hemorrhagic fever with renal syndrome and the pulmonary hantaviral syndrome [12-14]. In Romania the most frequent identified phenotypes are Puumala and Dobrava [15-17].

The pathogenesis of the hantavirus infections consists in an increased vascular permeability due to the over expression of the endothelial growth-factor.

Confirmation of the infections can be realised through direct methods (viral cultures, RT-PCR, in specialized laboratories) and indirect methods represented by the serological tests which highlight the antigens and the antibodies anti-Hantavirus type IgG/IgM [18]. Recent studies have shown the effectiveness of some rapid serological tests for the confirmation of the etiological diagnosis for the acute infection with Hantavirus, with high sensibility and specificity (FRET, TR-FRET) [19,20].

The disease's evolution is represented by two stages: the debut and the stage status.

The debut presents itself with a flu-like syndrome which can develop into severe forms until a shock.

The stage status can be classified into 5 stages [21,22]:

1. The fever stage, 3-7 days: sudden start, fever, headache, myalgia, arthralgia, queasiness, emesis, lumbar and abdominal pain.
2. The hypotonic stage, a couple of hours-2 days: facial hyperemia, sinus bradycardia, slight hypertension.
3. The oliguric stage, 4-7 days: hypertension, oligo-anuria.
4. The poliuric stage, days-weeks: with hydroelectrolytical imbalance and associated secondary infections.
5. The convalescence stage 2-3 months: in this time the renal function can be recovered completely in the most cases [21,22].

There is no etiological treatment for hemorrhagic fever with renal syndrome; it is only based upon hydroelectrolytical balance and the quick treatment of the secondary infections [2].

## Conclusions

If the patient presents in his personal history a possible infectious contact (with wild rodents, the bite of a rodent), flu-like symptoms (fever, myalgia, and headache), thrombocytopenia and secondary hemorrhagic syndrome and acute renal failure, you can suspect the diagnosis of hemorrhagic fever with renal syndrome. The confirmation of the diagnosis can be made through direct and indirect methods that are inaccessible because of the high costs, unavailable investigations in the public health systems. This fact leads to an almost impossible etiological diagnosis of this disease at

this specific time, which makes us wonder: How many cases of acute renal failure or hemorrhagic syndromes of unknown etiology are actually a secondary response to the infection with Hantavirus?

## References

1. Klempa B, Tkachenko EA, Dzagurova TK, Yunicheva YV, Morozov VG, Okulova NM. Hemorrhagic fever with renal syndrome caused by 2 lineages of Dobrava hantavirus, Russia. *Emerg Infect Dis* 2008; 14: 617-625.
2. Vaheri A, Vapalahti O, Plyusnin A. How to diagnose hantavirus infections and detect them in rodents and insectivores. *Rev Med Virol* 2008; 18: 277-288.
3. Mailles A, Abu Sin M, Ducoffre G, Heyman P, Koch J, Zeller H. Larger than usual increase in cases of hantavirus infections in Belgium, France and Germany, June 2005. *Euro Surveill* 2005; 10: 2754.
4. Faber MS, Ulrich RG, Frank C, Brockmann SO, Pfaff GM. Steep rise in notified hantavirus infections in Germany, April 2010. *Euro Surveill* 2010; 15.
5. Essbauer SS, Schmidt-Chanasit J, Madeja EL, Wegener W, Friedrich R. Nephropathia epidemica in metropolitan area, Germany. *Emerg Infect Dis* 2007; 13: 1271-1273.
6. SurvStatRKI. Berlin: Robert Koch Institute. Available from: <http://www3.rki.de/Survstat/QueryForm.aspx>
7. Tersago K, Verhagen R, Servais A, Heyman P, Ducoffre G. Hantavirus disease (nephropathia epidemica) in Belgium: effects of tree seed production and climate. *Epidemiol Infect* 2009; 137: 250-256.
8. Tersago K, Verhagen R, Vapalahti O, Heyman P, Ducoffre G, Leirs H. Hantavirus outbreak in Western Europe: reservoir host infection dynamics related to human disease patterns. *Epidemiol Infect* 2011; 139: 381-390.
9. Stenseth NC, Viljugren H, Jedrzejewski W, Mysterus A, Pucek Z. Population dynamics of *Clethrionomys glareolus* and *Apodemus flavicollis*: seasonal components of density dependence and density independence. *Acta Theriol* 2002; 47: 39-67.
10. Pucek Z, Jedrzejewski W, Jedrzejewska B, Pucek M. Rodent population dynamics in primeval deciduous forest (Bialowieza National Park) in relation to weather, seed crop and predation. *Acta Theriol* 1993; 38: 199-232.
11. Panculescu-Gatej RI, Sirbu A, Dinu S, Waldstrom M, Heyman P. Dobrava virus carried by the yellow-necked field mouse *Apodemus flavicollis*, causing hemorrhagic fever with renal syndrome in Romania. *Vector Borne Zoonotic Dis* 2014; 14: 358-364.
12. Heyman P, Ceianu CS, Christova I, Tordo N, Beersma M. A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005-2010. *Euro Surveill* 2011; 16.
13. Heyman P, Vaheri A, Lundkvist A, Avsic-Zupanc T. Hantavirus infections in Europe: from virus carriers to a major public health problem. *Expert Rev Anti Infect Ther* 2009; 7: 205-217.
14. Klempa B, Stanko M, Labuda M, Ulrich R, Meisel H, Krüger DH. Central European Dobrava hantavirus isolate from striped field mouse, *Apodemus agrarius*. *J Clin Microbiol* 2005; 43: 2756-2763.
15. Maftai ID, Segall L, Panculescu-Gatej R. Hantavirus infection-hemorrhagic fever with renal syndrome: the first case series reported in Romania and review of the literature. *Int Urol Nephrol* 2012; 44: 1185-1191.
16. Bi Z, Formenty PB, Roth CE. Hantavirus infection: a review and global update. *J Infect Dev Ctries* 2008; 2: 3-23.
17. Chassovnikarova T, Dimitrov H, Markov G, Mitev D. Distribution and habitat association of field mouse (*Apodemus agrarius*, Pallas, 1771) in national park Strandja. *Proc Balkan Sci Conf Biol Plovdiv* 2005; 428-436.
18. Gluhovschi G, Rosca A, Margineanu F. Hantavirus-specific IgG and IgM in Balkan Endemic Nephropathy (BEN) and chronic renal disease. *Facta Universitatis Med Biol* 2002; 9: 76-78.
19. Hepojoki S, Hepojoki J, Hedman K, Vapalahti O, Vaheri A. Rapid homogeneous immunoassay based on time-resolved Forster resonance energy transfer for serodiagnosis of acute hantavirus infection. *J Clin Microbiol* 2015; 53: 636-640.
20. Hepojoki S, Rusanen J, Hepojoki J, Nurmi V, Vaheri A. Competitive homogeneous immunoassay for rapid serodiagnosis of hantavirus disease. *J Clin Microbiol* 2015; 53: 2292-2297.
21. Vaheri A, Mills JN, Spiropoulou CF, Hjelle B. Hantaviruses. [www.eurosurveillance.org](http://www.eurosurveillance.org) Oxford Textbook of Zoonoses Biology Clinical Practice and Public Health Control Oxford University Press (2nd edn.) 2011: 307-322.
22. Heyman P, Vaheri A. Situation of hantavirus infections and haemorrhagic fever with renal syndrome in European countries as of December 2006. *Euro Surveill* 2008; 13: 18925.

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