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Chronic renal failure as a complication of hemorrhagic fever with renal syndrome in 17 years' old boy

Case Report

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Abstract: Hemorrhagic fever with renal syndrome (HFRS) is an acute infective multisystemic disease that commonly presents with fever, hemorrhage and acute renal failure. A 17-year-old boy presented with thrombocytopenia, profuse subconjunctival hemorrhage and anuric renal failure with fluid overload. The patient required continuous ambulatory peritoneal dialysis. He developed diuresis but did not recover renal function during reconvalescent period. Hantaan, Puumala, Seoul, Belgrade virus infection with haemorrhagic fever with renal syndrome was confirmed by serologic test.

Keywords: *Hemorrhagic fever with renal syndrome • Chronic renal failure*

1. Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an acute infective multisystemic disease that commonly presents with fever, hemorrhage and acute renal failure (ARF). The HFRS associated viruses are members of the genus Hantavirus, family Bunyaviridae. The same viruses can cause Hantavirus pulmonary syndrome (HPS) [1]. HFRS affects approximately 200,000 people each year predominantly in Asia. More than 30 different Hantaviruses have been distinguished so far and at least half of them are related to disease in humans. Several Hantavirus types can be found in Balkans: Belgrade/Dobrava, Puumala (causes epidemic nephropathy) and Seoul. Humans are being infected randomly via virus-containing aerosolized rodent excretions such as urine, feces or saliva [2-4].

Main pathogenesis mechanism, in development of HFRS, is vascular dysfunction as a result of capillary endothelial cells damage (hypotension, shock, acute tubulointerstitial nephritis and ARF) [5]. Incubation period ranges from 4 to 42 days. There are 5 stages of disease: fever, hypotension, oliguria, diuretic and reconvalescent stage [4].

Immunofluorescence assay, which is sensitive and group specific, has been widely used for diagnosis because of its ability to detect IgG and IgM antibodies. Enzyme immunoassays have also been developed, especially for sensitive detection of IgM antibodies [6,7].

Treatment is mainly supportive. There is some data that intravenous application of ribavirin lowers mortality and alleviates severity of the disease [8]. Rodent eradication in human environment is the most important preventive measure. Hantavirus vaccine is under development [9].

2. Case report

A 17-year-old boy became ill 10 days prior to admission with symptoms of headache, weakness, shivering and cough. He was treated symptomatically with ibuprofen. On the 5th day of the disease he got a fever of 39.5 degrees Celsius; day after vomiting (up to 15 times) and loose stools (5-6 times) developed. On the 7th day of the disease, he started to feel epigastric pain; swelling of the nose, eyelids and lips, dotted rush and hemor-

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rhages in the white of the eye had developed. On the 8th day of the disease, urine output reduced and the patient started to complain of pain in the lumbar region. Treatment was started with amoxicillin-clavulonate, oral rehydration solution and probiotics. On the 9th day of the disease he became afebrile and thirsty, but despite increased fluid intake (up to 3.5 liters per day), urine output remained low. On the 10th day of the illness, the following blood tests were performed: Sedimentation rate 24/, white blood cells 10.9 G/L (neutrophils 0.60), red blood cells 3.8 T/L, hemoglobin 110 g/L, hematocrit 0.34, platelet count 46 G/L. Blood urea nitrogen 30.2 mmol/L (<7.2), serum creatinine 675 μmol/L (<110). Aspartate aminotransferase 0.73 μkat/L (<0.40). Sodium 122 mmol/L (135-145), chloride 85 mmol/L (98-108). Urine: muddled, proteins 3+, hemoglobin 3+. After examination of a pediatric surgeon, who out ruled acute surgical condition, he was admitted to the Pediatric Intensive Care Unit.

Thirty days before admission, the boy went on a picnic on a nearby mountain – Fruska gora. Rats were sporadically observed in his house and surrounding area. Prior to this illness he was generally healthy. No hereditary diseases were noticed in his family.

On admission, 17-year-old boy, fully conscious, adinamic, afebrile, respiration rate 24/min, heart rate 120/min, blood pressure 136/92 mmHg, oxygen saturation - 98%. Body weight (BW) 63 kg (50.p), height 175 cm (50.p). The patient complained of pain to his back. Pale skin with petechial rush on face and back and hematoma on the tip of the nose. Discrete swelling of face and ankles. Profuse subconjunctival hemorrhage. Tongue covered. Abdomen in level of chests and soft, palpatory sensitive in epigastric and ileocoecal regions, liver palpable at 1.5 cm bellow right rib arch in medioclavicular line, spleen palpable 0.5 cm bellow left rib arch. Kidney lodges pain sensitive on succution. Rest of the physical examination was unremarkable.

Blood tests and other findings: C-reactive protein 40,3 mg/L, white blood cells 8,7 G/L (neutrophils 0,67), red blood cells 3,50 T/L, hemoglobin 102 g/L, hematocrit 0,27, platelet count 70 G/L, reticulocites 2,15%. Peripheral blood smear: anizocytosis and polychromic red blood cells, normal morphology of white blood cells with domination of neutrophils, rare and larger platelets. Serum electrolytes: sodium 109 mmol/L (135-145), potassium 4.4 mmol/L (4.0-5.2), ionized calcium 1.03 mmol/L (1.12-1.23), total calcium 1.95 mmol/L (2.10-2.55). Total proteins 50.93 g/L (60-80), albumins 28.72 g/L (32-45). Blood urea nitrogen 35.48 mmol/L (2.90-7.5), uric acid 582 μmol/L (124-448), creatinine 744.46...1197 μmol/L (62-106). Estimated creatinine clearance 15.6 mL/min...9.7 mL/min. Aspartate aminotransferase 1.04 μkat/L (0.17-0.68), lactate dehydrogenase 11.84 μkat/L (0-3.75). Values of blood sugar, lactates, inorganic phosphates, bilirubin, alanine aminotransferase, gamma glutamil transferase, creatine phosphokinase, prothrombin time, activated partial thromboplastin time, fibrinogen, blood gasses analysis and acid-base status in arterialized capillary blood were in referral ranges. Cultures of urine, stool and blood were negative. Urine slightly muddled, reddish, pH 8.0, urine specific gravity 1.005, proteins 5+; in sediment 55-60 red blood cells. Complement C3 0.63 g/L (0.8-1.6), C4 0.02 g/L (0.1-0.4). Values of C3 i C4 after 7 days were normal. Anti-GBM antibodies, ANCA, ANA - negative. Indirect immunofluorescence assay IgG on Hantaviruses (Hantaan, Puumala, Seoul, Belgrade) positive (>1:2048). Enzyme linked immunosorbent assay (ELISA) IgM test on Hantaviruses - Hantaan positive; Puumala borderline values. Hepatitis A virus, anti hepatitis C virus, hepatitis Bs antigen- negative. Specific Leptospira antibodies negative.

Chest X-ray: normal finding. Abdomen ultrasound: splenomegaly; appendix probably in retrocoecal position, partially compressible, of borderline size and wall thickness, with layerish appearance and slightly hyperemic. Discrete inflammatory reaction of surrounding adipose tissue. Walls of small intestines loops are hyperechogenic and thickened, up to 3mm. Urotract ultrasound: both kidneys enlarged, with hyperechogenic parenchyma, cortical-medullar border relatively clear, without dilation of pyelo-caliceal system. Both suprarenal lodges clear, bladder empty. Electrocardiogram: normogram, sinus rhythm, heart rate 60/min, Echocardiography finding- normal. Ophtalmogical examination: bilateral conjunctival suffusions.

After admission, anuric acute renal failure (ARF) with severe dilutional hyponatremia was diagnosed. Tenckhoff catheter for peritoneal dialysis was placed in general anesthesia and continuous ambulatory peritoneal dialysis (CAPD) was started. Beside this, conservative management of intrinsic ARF was introduced. Also, parenteral antibiotic therapy (cefatizidime), probiotics, per oral antimicotic as well as fraxiparine for prevention of deep veins thrombosis were started. Because of the severe nose bleeding in three times, anterior nose tamponade was performed. Clinical course was complicated with arterial hypertension (maximal values 170/100 mmHg) that was treated with calcium channel blocker - nifedipine. CAPD functioned well, dialysate was clear, ultra filtration satisfactory. From the 4th day of treatment edema resolved (BW 54kg). On 9th day of treatment urine output was reestablished and on the 11th day CAPD was discontinued. Patient was in good general condition without symptoms and discharged

from hospital on the 27th day of treatment. Laboratory values on discharge were as following: blood urea nitrogen 23.55 mmol/L (2.5-6), creatinine 330.57 μmol/L (40-70). Estimated creatinine clearance 35.5 mL/min. During following months he was under supervision of nephrologist, in good general condition and without symptoms, with blood pressure in referral range. Values of creatinine were around 190 umol/L (CCr 61.33 mL/min.). Renal ultrasound is normal.

3. Discussion

HFRS is usually caused by different Hantavirus serotypes. Clinical course, prognosis and lethality vary widely. Virus transfer from affected person to others does not occur in normal conditions.

The severity of the illness depends mainly on the Hantavirus strain. Infection with Korean hemorrhagic fever (Hantaan virus) and Balkan hemorrhagic fever (Dobrava virus) usually lead to severe cases, where as Seoul virus and Puumala virus usually cause mild to moderate forms of HFRS [4]. Belgrade virus, detected for the first time in 1989, always causes severe clinical form of illness [10].

The main reservoir of Hantavirus in nature are rodents. They live in communities without symptoms for long time. It is known that there might be multiple rodent hosts for individual virus species, and multiple viruses in a single host species. Some studies showed that Hantavirus infection can occur in other animals, such as cats, mice, dogs and cattle. Humans who live and work in near contact with infected rodents have greater risk to be infected. Studies showed higher percentage of seropositive individuals in this group in comparison to control groups [11].

Our patients probably got infected during a picnic in Fruska gora, where the presence of rodents infected with Hantavirus was noticed during previous years.

Clinical course of illness has five stages. Fever occurs in all patients and lasts for 4-6 days. In this stage beside flu-like symptoms and headache, subconjunctival hemorrhages and petechiae in axillary pits and soft palate can be observed. Characteristic sign is transitory miopathy documented in one third of patients. Also, bradicardia as well as atypical lymphocytosis and thrombocytopenia can develop. *Hypotension (shock) stage* develops in 11% of patients and lasts from few hours to two days, followed with *oliguric stage* that can be seen in 65% of patients in next 3-6 days. In this stage, the platelet count returns to normal values. The fourth stage is the *diuretic stage* that lasts from 2 to 3 weeks and the final one is *reconvalescent stage* during next 6 months [4]. Hypotension (shock) stage has not been observed in our patient.

Extra renal manifestations vary significantly – convulsions, myocarditis, severe gastrointestinal hemorrhage; liver, thyroid gland and pancreas as well as lungs (noncardiogenic pulmonary edema, bilateral infiltrates and pleural effusions) can also be affected [12].

The medical knowledge about HFRS and HPS has increased in the past years, resulting in the conclusion that both syndromes are partly overlapping. It is interesting that our patient had no clinical signs of lungs disease during illnes [12].

Differential diagnosis includes disseminated intravascular coagulation, hemolytic uremic syndrome/ thrombotic thrombocytopenic purpura, leptospirosis, malaria and dengue fever.

Course can be complicated with abdominal and pain in the back as a result of retroperitoneal hemorrhage. Our patient probably suffered from this complication [4]. Prognosis is usually good. Mortality in Puumala infection ranges from 0.1-0.4%, and in the case of Dobrafa infection from 7-12%. Mortality is higher for Belgrade Hantavirus (16.3%). Hantaan i Soeul subtypes cause severe forms of illness [13].

Renal function is usually fully reestablished immediately after acute phase of illness. Some authors established possibility of kidney sequelae in patients 1 to 3 years after HFRS [14]. Jovanovic et al. reported development of chronic renal failure (CRF) in 8.15% of cases among 135 adult patients treated of HFRS between 1989 and 2007 [14]. Makela et al. found pathological proteinuria and hypotension in some patients 3 to 7 years after illness, and Novo et al. reported only 1 case of CRF [15]. Only in the study of Glass et al. incidence of 33% of CRF after HFRS during five years follow-up was reported [16]. Some authors concluded that sequelae develop only after severe forms of illness, where as others found no connection between renal function disturbance and severity of illness in acute stages [17].

Our patient is one of the few patients that did not recover renal function during reconvalescent period. Hantaan and Belgrade serotypes that were isolated are cause of severe clinical course and probably responsible for this finding.

HFRS is a disease that normally appears as an epidemy when it is relatively easily diagnosed; however sometimes there are sporadic cases where it is harder to diagnose.We should bare in mind that infected rats' natural habitat is usually very near humans' habitats. Hantavirus infection can occur in other animals than rodents, such as cats, dogs and cattle!

References

[1] Peters CJ, Simpsons GL, Levy H. Spectrum of hantavirus infection:hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Annu Rev Med. 1999;50:531-545

[2] Jovanović D, Ignjatović Lj, Jovanović A. Hronična bubrežna insuficijnecija nakon preležane hemoragične groznice sa bubrežnim sindromom. Med Data Rev. 2011;2(2):151-154

[3] Mc Caughcy C, Hart CA. Hantaviruses. J Med Microbiol 2000;49(7):587-599

[4] Muranyi W, Bahr U, Zeier M, van der Woude FJ. Hantavirus infection. J Am Soc Nephrol. 2005;16:3669-3679

[5] Sirotin BZ, Keiser NP. On the history of the study of haemorrhagic fever with renal syndrome in eastern Russia. Nephrol Dial Transplant. 2001;16:1288-1289

[6] Maes P, Clement J, Gavrilovskaya I, Van ranst M. Hantaviruses: Immunology, treatment, and prevention. Viral Immunol. 2004;17:481-497

[7] Clement J, McKenna P, Groen J, Osterhaus A, Colson P, Vervoort T, van der Groen G, lee HW. Epidemiology and laboratory diagnosis of hantavirus (HTV) infections. Acta Clin Belg. 1992;22:984-990

[8] Chapman LE, Ellis BA, Koster FT, Sotir M, Ksiazek TG, Mertz GJ et al. Ribavirin Study Group: Discriminators between hantavirus-infected and –uninfected persons enrolled in a trial of intravenous ribavirin for presumptive hantavirus pulmonary syndrome. Clin Infect Dis. 2002;34:293-304

[9] Hjelle B. Vaccines against hantaviruses. Expert Rev Vaccines. 2002;1:373-384

[10] Obrenčević K, Jovanović D, Kovačević Z, Ignjatović Lj. Belgrade hantavirus infection is associated with the most severe clinical form of hemorrhagic fever with renal syndrome. BANTAO J. 2007;5(2):85-89

[11] Scharninghausen JJ, Faulde M, cavaljuge S. Hantavirus host/virus interactions within Southeast Europe. Bosn J Basic Med. 2004;4:13-18

[12] Beers MH, Berkow R. Infectious diseases; Viral diseases. In:The Merck manual of disgnosis and therapy, 17th Ed, Indianapolis, Wiley Publishers, 2005

[13] Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003;3(10):653-661

[14] Jovanović D, Škatarić V, Kovačević Z, marić M, Gligić A, Romanović R. Akutna bubrežna insuficijencija kod hemoragijske groznice sa renalnim sindromom. Vojnosanit Pregl. 1997;54(5):453-458

[15] Makela S, Ala-Houhala I, Mustonen J, Koivisto AM, Kouri T, Turjanman V. Renal function and blood pressure five years after puumala virus-induced nephropathy. Kidney Int. 2000;58(4):1711-1718

[16] Glass GE, Watson AJ, LeDuc JW, Childs JE. Domestic cases of hemorrhagic fever with renal syndrome in the United states. Nephron. 1994;68(1):48-51

[17] Elisaf M, Korakis H, Siamopoulos KC. Chronic renal dysfunction in hemorrhagic fever with renal syndrome patients. Ren Fail. 1993;15(5):623-627