

MIXED INFECTION - HANTAVIRUS HAEMORRHAGIC FEVER WITH RENAL SYNDROME AND HERPES SIMPLEX VIRUS ENCEPHALITIS: A CASE REPORT

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ABSTRACT

Introduction: This case report describes a patient treated at the Clinic of Infectious Diseases of University Hospital "St. George" Plovdiv, with two infections occurring at the same time – haemorrhagic fever with renal syndrome (HFRS) and herpes simplex virus (HSV) encephalitis. **Results:** A 53-year-old male presented with fever, flu-like syndrome and renal impairment with mild nitrogen elevation. The patient was treated at the Clinic of Nephrology for one week. Several hours after discharge he had three generalised tonic-clonic seizures and was admitted to the intensive care unit with status epilepticus and acute respiratory failure requiring intubation and mechanical ventilation for 4 days. Lumbar puncture results showed: white blood cells – $1.10^6/l$, glucose – 5.3 mmol/l, total protein – 1.6 g/l, increased immunoglobulin levels. The patient was transferred to the Clinic of Infectious Diseases with suspicion of viral encephalitis. HSV type 1 was detected in the cerebrospinal fluid by PCR. Due to suspected hantavirus infection, serum was examined and IgM and IgG

antibodies against the HFRS virus were detected by ELISA. Specific treatment with acyclovir was started and there was a rapid improvement in the clinical condition. Convulsions did not recur. Nitrogen levels normalised and there was a short period of polyuria. Thrombocytopenia quickly resolved without occurrence of haemorrhagic syndrome. In the course of the disease, the patient developed mild diarrhoeal syndrome and left thrombophlebitis. He was discharged clinically well with negative PCR results for HSV. In conclusion, we can assume that as a result of immunosuppression due to HFRS, HSV type 1 reactivated and led to herpes encephalitis.

KEYWORDS:

encephalitis, hantavirus, seizures, PCR, ELISA, herpes simplex virus

INTRODUCTION

Herpes encephalitis represents about 10-20% of all cases of sporadic viral encephalitis, with an incidence of about 2.3 cases per million per year and it has no seasonality (1). There is a bimodal age distribution – peak in the interval from 5 to 30 years and over 50 years of age. Herpes simplex virus (HSV) type 1 causes over 95% of cases (2). PCR examination for viral deoxyribonucleic acid (DNA) in the cerebrospinal fluid (CSF) is the gold standard for diagnosis (3). Mortality is about 70% without etiological treatment. Even with treatment, mortality remains high – 18%, and some of the patients develop severe neurological deficits (1, 4).

Haemorrhagic fever with renal syndrome (HFRS) starts with flu-like symptoms but it can progress to shock, haemorrhage and renal failure. Seizures or focal neurological symptoms occur in 1%. Diagnosis is confirmed by serological tests and PCR. Mortality is 6-15% (5). The disease occurs mainly in Asia and Europe, accounting for about 100,000 cases per year (6). Severe forms of HFRS (caused by Hantaan, Seoul, and Dobrava viruses) are characteristic of Korea and the Balkan Peninsula countries (5). In Bulgaria the disease has been reported since 1953. HFRS cases are mainly reported in the mountainous regions of the country (7). For the period 2013-2014, 23 cases of HFRS were observed and 69.6% were caused by the Dobrava-Belgrade virus (DOBV)

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and 30.4% by the Puumala virus. The clinical presentation due to DOBV was more severe (8). In Bulgaria the seroprevalence of hantaviruses is estimated to be 3.1% (9). Although the disease is well-known in endemic regions, it can be found in non-endemic as well (10).

MATERIAL AND METHODS

This case report describes a patient with hantavirus haemorrhagic fever with renal syndrome and herpes encephalitis occurring simultaneously. The patient was treated at the Clinic of Infectious Diseases, University Hospital "St. George" Plovdiv from 6 March to 22 March, 2017. The following methods were used – clinical observation, laboratory, microbiological, serological, molecular tests and imaging techniques.

RESULTS

I.I.C., a 53-year-old male diagnosed with nephritis tubulointerstitialis was treated between 23 February and 2 March 2017 at the Clinic of Nephrology. The patient was admitted with fever of 39°C, chills, oliguria and asthenodynamia. Laboratory examinations showed proteinuria and erythrocyturia, creatinine 264 mg/dl, urea 17.8 mg/dl; kidney ultrasound revealed diffuse bilateral parenchymal process; lung computed tomography (CT) indicated small pleural effusions predominantly in the right side.

On the day of discharge, the patient had three generalised tonic-clonic convulsions with oral secretion and tongue injury. He was transported to the Emergency Department of the University Hospital "St. George" Plovdiv, where he had another seizure with focal onset affecting the left side of the face, rapid generalisation, stertorous breathing, cyanosis and severe tonic phase. The patient was admitted to the ICU with status epilepticus, acute respiratory failure, Glasgow Coma Scale (GCS) - 5 points, requiring intubation and mechanical ventilation for 3 days, Depakine, Dormicum and phenobarbital infusions. Lumbar puncture (LP) was performed and the patient was transferred to the Clinic of Infectious Diseases on 6 March due to suspected viral encephalitis. Physical examination showed severe medical condition. The patient was afebrile, conscious,

orientated, with bradypsychia and bradylalia, no signs of meningeal irritation, normal symmetrical tendon reflexes, without Babinski sign and no cranial nerve palsy. There was a massive subconjunctival haemorrhage in the left eye. Respiratory system – normal breathing; cardiovascular system – normal sinus rhythm, RR 150/90 mmHg, 80 beats/min; abdominal status – painless, hepatosplenomegaly, Pasternacki's sign – negative.

Laboratory tests showed:

- mild anaemia in the course of disease with decreased haemoglobin of 101.109 g/l;
- leucocytosis of $16.10^9/l$ with neutrophilia and lymphopenia;
- transient thrombocytopenia of $56.10^9/l$;
- increased erythrocyte sedimentation rate (ESR) – 52 mm/h and C-reactive protein (CRP) – 157 mg/dl;
- mild nitrogen elevation during the first days of hospital stay with 207 mg/dl creatinine and 15 mg/dl urea. Significant electrolyte disturbances were not observed. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were slightly elevated – 105 and 77 UI/l, respectively, and low albumin levels were recorded throughout the whole hospital stay of up to 28 mg/dl;
- coagulation tests – slightly decreased prothrombin time (PT) and activated partial thromboplastin time (APTT); normal fibrinogen and transient increase of D-dimers. Multiple urine tests showed proteinuria, presence of erythrocytes, leukocytes and single granular casts;
- CSF findings are presented in Table 1 and 2.

Table 1. Cerebrospinal fluid examination.

CSF findings	I lumbar puncture (3 March)	II lumbar puncture (20 March)
Total protein (g/l)	1.6 ↑	0.37
Glucose (mmol/l)	5.4 ↑	2.7
White blood cells ($\times 10^6/l$)	1	3

Table 2. Immunoglobulin results in the initial lumbar puncture and serum (3 March)

Immunoglobulins	CSF (mg/l)	Serum (g/l) - within normal range
IgA	121.28 ↑	3.84
IgM	31.34 ↑	2.21
IgG	375.17 ↑	13.9
IgE	-	5.5

Microbiological examination yielded negative CSF culture; *Enterococcus faecium* was isolated from urine and ESBL-producing *Serratia marcescens* from blood culture. The patient was further investigated for HBsAg and HIV-Ab which were negative.

Two etiological agents were identified at the National Centre of Infectious and Parasitic Diseases, Sofia, as follows:

- 9 March: first serum sample – IgM antibodies against the HFRS virus were not detected by ELISA;
- 20 March: second serum sample – IgM and IgG antibodies against the HFRS virus were detected by ELISA;
- 9 March: first CSF sample – positive PCR results for HSV-1 and negative for HSV-2;
- 22 March: second CSF sample – PCR results for HSV-1 after acyclovir treatment were no longer positive.

Imaging: on the day of admission was performed head CT scan showing brain oedema. An electroencephalogram (EEG) was also performed in the middle of the hospital stay indicating no abnormalities.

The treatment was prolonged and complex comprising of etiological, pathogenetic and symptomatic drugs. Administration of acyclovir was adjusted according to renal function to 400 mg IV 3 times daily for 23 days; Depakine infusions during the first days were replaced with oral administration for 2 weeks; antibiotics - ceftriaxone 2 g daily for 10 days, vancomycin 1 g/8 hours for 10 days, metronidazole 500 mg/8 hours for 5 days and ciprofloxacin 200 mg/12 hours for 7 days targeting the microorganisms isolated from blood and urine as well as the

diarrhoeal syndrome, superficial and deep thrombophlebitis that developed during the hospital stay.

DISCUSSION

The mixed infection with HFRS and herpes encephalitis occurred as a severe disease but with rapid clinical improvement. Seizures did not recur. Nitrogen elevation associated with HFRS was overcome and short-term polyuric stage ensued for 3-4 days with 6 l/daily. There was a mild diarrhoeal syndrome. Thrombocytopenia quickly resolved without occurrence of haemorrhagic syndrome. During the course of the disease the patient developed iatrogenic phlebitis on the right cubital vein and deep left thrombophlebitis. He was discharged fully recovered with negative PCR results for HSV. Based on the clinical presentation, serological and molecular tests, it was assumed that the patient had mixed infection with HSV type 1 and HFRS virus. To our knowledge, no other cases of such mixed infection were described in the literature. In a study by Shin et al. it was proven that hantaviruses are involved in the modulation of innate immune responses in the brain (11). Host immune responses affect the onset of HSV disease, the severity of infection and recurrence rates (2).

CONCLUSION

In the case of our patient, we can assume that as a result of immunosuppression caused by HFRS, HSV-1 reactivated and led to herpes encephalitis.

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