CASE REPORT / OLGU SUNUMU

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A Case of Mild Encephalitis/Encephalopathy with a Reversible Splenial Lesion (MERS) Caused by Hantavirus

Hantavirüsün Neden Olduğu Geri Dönüşlü Spleniyal Lezyonlu Hafif Ensefalit/Ensefalopati (MERS) Olgusu

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Abstract

Hantavirus, which is seen globally, is a zoonotic pathogen that causes severe clinical pictures such as fever, thrombocytopenia-related hemorrhages and acute renal failure in humans. Their natural hosts are rodents, insectivorous animals and bats. Mild encephalitis/encephalopathy with a reversible splenial lesion, in which many viral infections including Hantavirus play a role in the etiology, is an encephalitis/encephalopathy condition. In this case report, it was aimed to draw attention to the rapidly progressing and mortal Hantavirus infection.
Keywords: Hantavirus, encephalopathy, thrombocytopenia

Öz

Global olarak görülen Hantavirüs insanlarda ateş, trombositopeniye bağlı kanamalar ve akut böbrek yetmezliği gibi ciddi klinik tablolara yol açan zoonotik bir patojendir. Doğal konakçıları kemirgenler, böcek yiyen hayvanlar ve yarasalardır. Hantavirüs dahil birçok viral enfeksiyonun etyolojide rol aldığı "mild encephalitis/encephalopathy with a reversible splenial lesion" bir ensefalit/ensefalopati durumudur. Bu olgu sunumunda hızla ilerleyen ve mortal seyreden Hantavirüs enfeksiyonuna dikkat çekmek amaçlanmıştır.
Anahtar Kelimeler: Hantavirüs, ensefalopati, trombositopeni

Introduction

Hantavirus, a negative single-stranded RNA virus, is a member of the Bunyaviridae family. In nature, they are carried by rodents, insect-eating animals and bats. Transmission is usually by oral, mucosal or inhalation route as a result of contamination of the environment with the excrement of sick animals, and there is rarely a recent rodent bite history. In humans, they usually present with two different acute febrile illnesses, one is hemorrhagic fever with renal syndrome (RSHA) with bleeding diathesis and renal failure ranging from petechiae to hemorrhage, and the other is Hantavirus pulmonary syndrome (HPS) characterized by the development of cardiac arrhythmias and acute respiratory distress syndrome. While 1,000 cases of HPS are reported worldwide each year, more than 100,000 cases of RSHA are estimated to be[1,2]. Hantavirus infection was first identified in our country in 2009, and patients with RSHA have been reported every year since then[3]. This disease cannot be differentiated from Crimean-Congo hemorrhagic fever (CCHF) and Leptospira infection due to the similarity of its routes of transmission and clinical course such as fever, bleeding diathesis, and nephropathy[4]. Today, depending on the developments in laboratory tests, the rate of identification of infectious agents has increased. This makes it possible to detect the causative agent in many clinical situations.

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Encephalitis/encephalopathy syndrome, known as mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is generally characterized by mild central nervous system (CNS) symptoms such as impaired consciousness, seizures and headache. As a result of the evaluation of patients with similar cranial lesions in a retrospective study conducted for the first time in 2004, the importance of upper respiratory tract infection agents such as influenza, rotavirus and *Moraxella* in the etiology of MERS was emphasized[5].

In conclusion, although MERS has a mild clinical course and tends to heal, it should be kept in mind that infectious agents with high mortality, such as Hantavirus, may be the cause. With this case report, we wanted to draw the attention of physicians to this issue.

Case Report

A 49-year-old male patient living in the Black Sea countryside was referred to our hospital with complaints of weakness, blurred consciousness, occasional speech deterioration, hypotension, and fever for three days. The patient's self-care was poor. He had no known chronic disease. In his detailed anamnesis, there was no contact with any ticks or other insects, no consumption of spoiled meat or food, no use of drugs, substances or stimulants in the last month. However, he had a history of hospitalization due to substance use at a toxic dose a year and a half ago, and cleaning the coal pit a week ago. There were no complaints of diarrhea, nausea, vomiting, and dysuria.

The general condition of the patient was moderate, he was conscious, cooperative, oriented, blood pressure was 100/80 mmHg, temperature was 37.5 °C, oxygen saturation (sO_2) was 98%, pulse rate was 93/minute, and respiratory rate was 25/minute. In his examination, no visible soft tissue lesion or bleeding focus was detected. In head and neck examination, the oropharynx was normal, nuchal rigidity was absent, and lymphadenopathy was not detected. By listening, respiratory sounds were normal, heart was rhythmic and no additional sounds or murmurs were detected. There was no rebound tenderness or abdominal guarding. On inspection, diffuse petechial rashes intensified by pressing were observed on the abdominal skin.

Possible preliminary diagnoses were Coronavirus disease-19 (COVID-19) due to fever and pandemic, thrombotic thrombocytopenic purpura (TTP) due to thrombocytopenia and rashes, hemolytic uremic syndrome (HUS) due to thrombocytopenia and renal failure, Hantavirus infection which was endemic in the Black Sea region, Leptospira infection, and CCHF. The results of laboratory tests were as follows: leukocyte (white blood cell) count: 13350 10^9/l, thrombocyte count: 13.000 10^9/l, hemoglobin: 19.1 g/dl, creatinine: 2.66 mg/dl, sodium: 127 mmol/l, aspartate aminotransferase: 122 U/l, alanine aminotrasferase: 43 U/L, lactate dehydrogenase: 809 U/l, creatine kinase: 1351 U/l, glucose: 128 mg/dl, C-reactive protein: 45 mg/l, proclacytonin: 16, ferritin: >2000 µg/l, D-Dimer: 7133 ng/ml, prothrombin time: 17.2 seconds, international normalized ratio: 1.46, sO_2 in venous blood gas (sO_2): 14.6%, partial oxygen pressure: 18 mmHg, partial carbon dioxide pressure: 44 mmHg, and bicarbonate: 15.5 mmol/L. The COVID-19 polymerase chain reaction (PCR) test was negative and the thorax computed tomography (CT) was interpreted as normal.

In the differential diagnosis, Severe acute respiratory syndrome-Coronavirus-2 infection was excluded, since there was no lung involvement radiologically compatible with COVID-19 and COVID-19 PCR test was negative. In the evaluation made by the hematology department, the diagnosis of HUS was ruled out because the indirect Coombs test was negative, and TTP was excluded because he did not have anemia. The patient's elevated hemoglobin level was attributed to dehydration. In the diagnosis, Hantavirus and Leptospira infections were considered, as there might be contact with mouse excrement or inhalation of particles scattered in the environment during cleaning due to a history of charcoal cleaning. In addition, due to the prevalence of CCHF in the Black Sea region, the possibility of tick contact during coal mine cleaning brought CCHF infection to mind.

Lumbar puncture was planned for the differential diagnosis of encephalitis due to the occasional change in consciousness in the patient, but it could not be performed due to thrombocytopenia. A lesion in the corpus callosum splenium was seen in the cranial magnetic resonance imaging (MRI) (Figure 1). In the evaluation

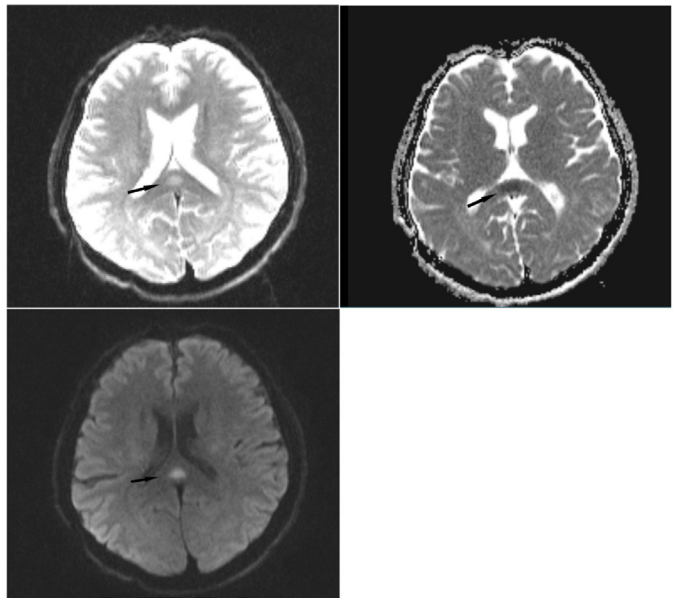

Figure 1. Diffusion magnetic resonance and T2W imaging show a lesion showing diffusion restriction in the splenium of the corpus callosum, which is hyperintense on b1000 and T2W images and hypointense on the ADC map

made by the neurology department, it was stated that it might be secondary to viral infections.

In conclusion, it was stated that thrombocytopenia was not related to TTP and HUS after evaluation by the hematology department, that the current situation might be secondary to viral infection, and that corpus callosum lesion seen in cranial MRI after evaluation by the neurology department might be secondary to viral infection. The patient was hospitalized with the preliminary diagnoses of CCHF, Leptospirosis, Hantavirus infection, HUS and TTP. Intravenous ceftriaxone 1x2 g/day was started for Leptospirosis, which was the antibiotic that could be reached as soon as possible in the hospital. Thrombocyte replacement treatment was performed. In the clinical follow-up of the patient, desaturation in the form of intermittent attacks, loss of vision, absence of light reflex, and change in consciousness were observed. Considering cranial bleeding in the patient who developed agitation, consultation was requested from neurosurgery, neurology and anesthesia units. Brain CT was performed and no bleeding was detected. In the control hemogram results, thrombocytopenia continued. The patient, who developed anuria during the follow-up, was taken to the dialysis program because of deep acidosis. Methyl alcohol level was measured in the patient because of his history of substance use. Tests for Hantavirus, Leptospira and CCHF were planned. Respiratory arrest developed in the tenth hour after the patient's admission, and the patient who was intubated and taken to the intensive care unit died four hours later. Since the examinations for Hantavirus, CCHF and Leptospira were performed outside the institution, the patient's examinations were concluded one week after he died. Hantavirus IgM and IgG were positive, no causative agent was detected in the tests for CCHF and Leptospira.

Discussion

Hantavirus is a member of the Bunyaviridae family and consists of negative single-stranded RNA. It is carried in nature by rodents, insect-eating animals and bats. It generally survives in their natural hosts without causing disease[1,2]. Unlike other Bunyaviridae members, Hantaviruses do not use an arthropod vector for transmission. Hantaviruses are also often closely related to a single rodent species. Accordingly, the temporal and spatial distributions of human Hantavirus infections reflect the distribution of rodent hosts[3]. Depending on the species, the disease course associated with RSHA can range from mild to severe. RSHA caused by Hantaan virus, Amur virus or Dobrava-Belgrade virus is severe and the mortality rate is 10-15%. Caused by Puumala virus, RSHA has a mild clinical course, is defined as epidemic nephropathy (EN), and its mortality rate is below 1%. While Andes virus (ANDV) is associated with severe HPS with a mortality of 30-50%, Prospect Hill virus is not associated with human disease[1,2,4]. Our patient presented with a complaint of fever, he had petechiae on the skin, as a result of laboratory tests acute renal failure was detected and the disease's course was mortal.

The risk of contracting Hantavirus from rodents is related to the proximity of contact. Natural disasters such as floods and earthquakes can facilitate human-rodent contact. The rainy and forested nature of the Black Sea Region creates a suitable environment for Hantavirus transmission. The disease is generally transmitted by inhalation of aerosols formed as a result of contamination of the environment with the excreta (saliva, urine and faeces) of sick animals. It can also be transmitted orally, through mucous membranes and damaged skin[2,6]. Person-to-person transmission of Hantaviruses is rare and is limited to only one type of Hantavirus, ANDV. The time between exposure to Hantavirus and the onset of symptoms ranges from 1 to 6 weeks, with an average of 14 to 17 days[7]. In our patient, it was thought that the particles might be inhaled by scattering during the cleaning of the coal pit a week ago.

There is evidence that Hantavirus has the ability to affect the CNS in patients with EN[8,9]. In the review by Hautala et al.[8,10], the importance of CNS symptoms and vision loss is emphasized. They mention that more than 90% of the patients have headaches and more than 80% have visual problems in CNS involvement. In addition, it was stated that there were patients with acute and complete vision loss similar to the temporary vision loss seen in our patient, that pituitary bleeding was detected in these patients, and that hormonal failure developed due to the pituitary gland being affected. In some patients with pituitary gland hemorrhage, it was stated that the sudden and complete loss of vision, which was estimated to be caused by optic chiasm compression, recovered in a short time. Our patient also experienced sudden vision loss in the form of attacks and his visual function was normal between attacks.

Hantaviruses cause vascular leakage in the target organ by affecting the vascular structure. Target organs are mostly lung, heart, kidney and vascular endothelium in lymphoid organs. As a result of fluid leakage into the extravascular area, hypovolemia and hypotension develop and organ damage occurs[11]. While our patient had sudden hypotension attacks and a normal clinical course between attacks, shock developed in the following hours. It was evaluated as hemorrhagic shock due to the possibility of internal bleeding.

In the cranial MRI performed due to the change in consciousness of our patient, a MERS-specific lesion was observed. MERS was an entity that was first defined by evaluating the clinical, laboratory and radiological features of 22 patients with corpus callosum splenium lesion in the retrospective study of Tada et al.[5]. MERS is a radiologically

detected condition that can usually be triggered by infectious agents such as Influenza virus, Rotavirus, Mumps virus, *Mycoplasma pneumonia* or *Legionella pneumophilia*[5,12,13]. However, apart from infection, it is also associated with various causes such as high altitude, cerebral edema, epileptic seizures, discontinuation of antiepileptic drugs and metabolic disorders. Therefore, it is stated that MERS is an infection-related encephalopathy syndrome rather than encephalitis. Various hypotheses regarding the MERS mechanism include intramyelin axonal edema, infiltration of inflammatory cells, activation of the immune system, oxidative stress, and fluid imbalance[14]. As a result of the evaluation of our patient by the neurology clinic, it was stated that the lesion seen on cranial MRI might be secondary to viral infections.

The MERS usually presents with altered consciousness, seizures, drowsiness, headache, abnormal speech, visual hallucinations and ataxia[5]. In the review by Tuscano et al.[15], transient blindness was reported as the initial symptom of MERS in a few children. Our patient's altered consciousness, temporary loss of vision, meaningless speech, absence of light reflex, and hypotensive episodes were consistent with the neurological symptoms of MERS. In addition, it is emphasized in the literature that the presence of hyponatremia in patients with MERS is related to the elevation of IL-6, which has an important role in vasopressin release in patients[14]. Our patient also had significant hyponatremia, but since the IL-6 level was not checked and control cranial MRI was not performed, no comment could be made on whether the hyponatremia was due to high IL-6 level or pituitary bleeding, which was one of the pathogenesis found in the literature.

Due to clinical similarities in infectious diseases, the diagnosis should be supported by laboratory tests in order to plan the treatment correctly. For this, the disease must come to mind. We believe that surveillance studies on this subject will guide the clinician in making the diagnosis and will be useful in the control of diseases.

For diagnosis, serum samples were sent to the Turkish General Directorate of Public Health, National Arboviruses and Viral Zoonosis Laboratory, Microbiology Reference Laboratories and Biological Products Department. In serology, IgM [indirect immunofluorescence test-(IFA)] and IgG (IFA) were positive. It was evaluated as acute Hantavirus infection. Since Hantavirus causes short-term and low-level viremia in the blood, the sensitivity of methods such as real time-PCR decreases compared to serological methods. This makes it more meaningful to monitor serological responses in the laboratory diagnosis of the disease[16].

There is no proven antiviral treatment for Hantavirus. In most of the patients, symptomatic support such as thrombocyte replacement and hemodialysis gain importance, depending on the affected state of the patients. The aim of treatment is to maintain adequate perfusion in organs and tissues. For this purpose, hypotension, shock, oliguria-anuria, bleeding, respiratory failure and electrolyte disturbances should be followed up closely.

Due to kidney and corpus callosum involvement in our patient, we searched simultaneously the keywords "Hantavirus" and "corpus callosum splenium". We could not find a reported corpus callosum splenium lesion in a patient with Hantavirus infection.

Conclusion

In conclusion, Hantavirus infection is clinically similar to many diseases and should be considered in the differential diagnosis. Its treatment is symptomatic and should be carefully managed due to its fulminant course.

Ethics

Informed Consent: Consent was obtained from the relatives of the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., N.T.T., A.M.Ş., Concept: E.A., N.T.T., Design: E.A., Data Collection or Processing: E.A., N.T.T., Analysis or Interpretation: E.A., N.T.T., A.M.Ş., Literature Search: E.A., Writing: E.A.

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