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Panhypopituitarism Following Hemorrhagic Fever with Renal Syndrome Due to Hantavirus

Hantavirüse Bağlı Renal Sendromlu Hemorajik Ateş Sonrası Panhipopitüitarizm

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ABSTRACT

Introduction: Hemorrhagic fever with renal syndrome (HFRS) is an acute viral disease caused by viruses that belong to the genus Hantavirus. Hantaviruses produce a spectrum of illness characterized by fever, circulatory collapse, hemorrhages, and renal failure. Pituitary ischemia/infarction and necrosis are known causes of hypopituitarism, often remaining unrecognized because of subtle clinical manifestations. In this report, we present a case of a 60-year-old male patient who was referred to the emergency department (ED) for unexplained hypoglicemia, with panhypopituitarism following HFRS.

Case Report: We, hereby, present a 60-year-old male patient admitted to the ED because of unexplained hypoglicemia, with panhypopituitarism following HFRS. Blood tests revealed panhypopituitarism and anti-hantavirus IgM and IgG positivity. Hormone replacement theraphy was initiated, and he was discharged for outpatient follow-up with total recovery.

Conclusion: Panypopituitarism is an extremely rare complication of HFRS. Emergency medicine, internal medicine, and infectious diseases specialists should be aware of this complication to reduce mortality and morbidity.

ÖZET

Giriş: Renal Sendromlu Hemorajik Ateş (RSHA), Hantavirüs cinsine bağlı virüslerce oluşan akut bir viral hastalıktır. Hantavirüsler; ateş, dolaşım bozukluğu, kanama ve renal yetmezlik ile karekterize bir hastalık spektrumuna neden olurlar. Hipopitütiarizmin bilinen nedenleri pitüiter iskemi/infarkt ve nekroz olup klinik özelliklerinin belirsiz olmasından dolayı genellikle farkedilemezler. Bu yazıda, acil servise (AS) açıklanamayan hipoglisemi nedeni ile sevkedilen RSHA sonrası panhipopitüitarizm gelişen 60 yaşına erkek olgusunu sunduk.

Olgu Sunumu: Biz acil servise RSHA sonrası gelişen panhipopitutuarizm beraber AS'ye açıklanamayan hipoglisemi ile başvuran 60 yaşında bir erkek hasta sunduk. Hastanın kan tetkiklerinde panhipopituitarizm ve anti-Hantavirüs IgG ve IgM pozitifliği tespit edildi. Hormon replasman tedavisi başlandı ve hasta ayaktan takibe alınarak tam iyileşme ile taburcu edildi.

Sonuç: Panhipopituitarizm RSHA sonrası çok nadir görülen bir komplikasyondur. Morbidite ve mortaliteyi azaltmak için; acil tıp, dahili tıp ve enfeksiyon hastalıkları uzmanları bu komplikasyona karşı uyanık olmalıdırlar.

Keywords: Hemorrhagic fever with renal syndrome, panhypopituitarism, hantavirus infections

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Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an acute viral disease caused by RNA viruses that belong to the genus Hantavirus, family Bunyaviridae (1). Currently. there are seven hantaviruses known to be associated with HFRS; Hantaan virus (HTNV) in Asia and Dobrava-Belgrade virus in Europe cause the most severe form of HFRS with a mortality rate from 3% to 12% (2, 3). Two acute febrile diseases could result from infection with Hantavirus: Korean hemorrhagic fever, caused by Hantaan

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virus and epidemic nephropathy, caused by Puumala virus. Both infections are prevalent in Asia (Korea) and Europe (Scandinavia and the Balkan peninsula). The hantaviruses are transmitted by rodents and present a special danger to humans who have close contact with field rodents (field workers and soldiers) (4).

The clinical course of HFRS is characterized by fever, circulatory collapse with hypotension, hemorrhages, and renal failure. The disease progresses through the characteristic five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. Most HFRS patients recover completely and complications are rare. Pituitary atrophy, secondary empty sella, and clinically overt hypopituitarism have been reported only sporadically in patients who recovered (4-9). These findings suggest that patients with HFRS have pituitary hemorrhage and subsequent necrosis with permanent pituitary failure. Here, we describe a patient with panhypopituitarism following HFRS and aim to underline the importance of attention of both emergency and internal medicine specialists in the diagnosis of this rare entity.

Case Report

A 60-year-old man was referred to our emergency department (ED) for further evaluation of hypoglicemia. He was a farmer and living alone at a village. He was brought to the ED 12 days ago with fever and diarrhea with decreased urine output and was hospitalized in the Infectious Diseases Clinic. From his past medical records, his baseline biochemical and hematological characteristics 1 month ago and at admission are shown in Table 1. Because of impaired renal function, he had undergone haemodialysis several times. He had ampicilin-sulbactam and later cephtriaxone treatment to cover for bacterial infections like Gram negative sepsis, leptospirosis, and enteric fever. Blood samples (acute and convalescent) were subsequently tested for anti-hantavirus immunoglobulin IgM and IgG and Crimean-Congo haemorrhagic fever. Blood culture tests were all negative. After 2 weeks of treatment, he was discharged from the hospital and he was advised to take care and to return for follow-up examinations. Soon after discharge from the hospital, he presented to the ED because of confusion and severe hypoglicemia (blood glucose: 26 mg/dL).

Physical examination on presentation revealed blood pressure 90/60 mmHg, pulse rate 100/min, respiratory rate 16 breaths/min, and temperature 37.7°C. Except his neurologic status, rest of the physical exam was normal. He was hospitalized and infusion of hypertonic glucose was initiated. The baseline laboratory findings revealed hyperkalemia. The patient was evaluated for panhypopituitarism. His hormone panel is shown in Table 2. Magnetic resonance imaging (MRI) findings was normal. Empty sella or pituitary hemorrhage were not detected in the MRI. We obtained the results for anti-hantavirus immunoglobulin IgM and IgG and they were both positive. The patient's clinical picture was consistent with hemorrhagic fever with renal syndrome. After consultation with the infection clinic, acute phase was resolved without any therapy. A hormone replacement therapy was initiated and he was discharged for outpatient follow-up.

Discussion

Hantaviruses have the potential to cause two different types of diseases in human: HFRS and hantavirus pulmonary syndrome

Table 1. Biochemical characteristics of patient two weeks ago and on admission

Parameters	Two weeks ago	On admission	Normal range
WBC (10^3/μL)	12.7	5.45	4000-10000
Hemoglobin (g/dL)	12.8	11.1	12-17
PLT (10^3/μL)	42	248	130-400
Glucose (mg/dL)	79	26	74-109
BUN (mg/dL)	102.8	34	7.8-22.8
Creatinine (mg/dL)	7.12	3.34	0.7-1.3
AST (U/L)	203	59	0-40
ALT (U/L)	216	42	0-41
GGT (U/L)	20	45	8-61
Total Bilirubin (mg/dL)	0.79	0.26	0.0-1.2
Direct Bilirubin (mg/dL)	0.45	0.18	0-0.3
Indirect Bilirubin	0.34	0.08	0.0-0.7
Creatinin Kinase(IU/L)	188	48	39-308
LDH (U/dL)	490	432	135-225
CRP(mg/dL)	12.7	13.5	0-0.8

WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine transaminase; BUN: blood urea nitrogen; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; CRP: C-reactive protein

Table 2. Hormone test results

Parameters	Patient Values	Normal Values
Cortisol (μg/dL)	13.52	4.6-22.8
ACTH (pg/mL)	<1	5-60
FSH (mIU/mL)	0.47	1.9-18.9
LH (mIU/mL)	0.00	1.7-9.6
Prolactin (ng/mL)	0.22	2.1-17.7
Total Testosterone (ng/dL)	0.00	241-827
Growth Hormone (ng/mL)	0.07	0-8

ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH; follicle-stimulating hormone

(3). Hypopituitarism associated with hemorrhagic fever with renal syndrome has not been reported elsewhere (4-8). The exact mechanism of the hypopituitarism is unknown. The possible mechanisms are as follows: Hypopituitarism may be caused by hemorrhage due to low platelet count and/or increased microvascular permeability, ischemia during hypovolemic shock and oliguric phase of hemorrhagic fever with renal syndrome, and necrosis due to direct cytopathic viral effect and bacterial embolization (8).

Pekic et al. (8) described the first report of hypopituitarism that developed as a sequel of HFRS in the region of the Balkans and then sporadic cases have been presented. They reported three cases

that developed hypopituitarism as a late complication of HFRS. Stojanovic et al. (8) reported the prevalance of hypopituitarism among HFRS survivors. In 60 adults who recovered from HFRS, they reported five (8.3%) had multiple pituitary hormone deficiencies. They found a high prevalence of hypopituitarism (18.3%) in patients who recovered from HFRS many years ago. Javanovic et al. (9) also presented a patient with the development of chronic renal insufficiency and hypopituitarism as complications that had been diagnosed 6 years after hantavirus infection. All of these cases had developed hypopituitarism as a late complication of HFRS, whereas hypopituitarism developed a month later in our patient. In our case, pituitary hemorrhage and atrophy findings were not detected in the MRI. We postulated that panhypopituitarism in our patient seems to be related to ischemia during hypovolemic shock and oliguric phase of hemorrhagic fever with renal syndrome.

From our country, early case reports identified a hantavirus epidemic (laboratory confirmed) in February 2009 that involved 12 persons in Bartin and Zonguldak in Western Turkey near the Black Sea (10). Sarıgüzel et al. (11) also described hemorrhagic fever with renal syndrome complicated by panhypopituitarism. The clinical findings of the patient were more compatible with septic shock requiring inotropic therapy. They performed serotyping by using focus reduction neutralization tests and results confirmed the infection by Dobrava-Belgrade virus *Apodemus flavicollis*. Our patient was more stable. We could not determine the serotype of the causative agent for technical reasons. Because hantaviruses are transmitted by rodents and our patient was a farmer living alone in poor conditions, he possibly had the infection via aerosolized excretions of virus-hosting rodents.

To our best knowledge, this is the second case report of a hantavirus infection complicated with panhypopituitarism in our country, although it is a non-endemic area for hantavirus infection. Patients with acute febrile illness presenting with thrombocytopaenia, renal failure, and elevated liver enzymes should be tested for anti-hantavirus IgM and IgG. Hantavirus infection should be considered in the differential diagnosis presenting with panhypopituitarism, particularly in patients living in poor conditions and among farmers. Demographics, history of animal contact, and outdoor activity are important patient details to be recorded in areas non-endemic for hantavirus infections. We think hypopituitarism due to HFRS is more common than recognized in persons living in poor sanitary conditions and presenting to the ED with complaints of fever.

Conclusion

Hemorrhagic fever with renal syndrome is an acute viral disease characterized by fever, circulatory collapse with hypotension, hemorrhages, and renal failure. As an extremely rare complication, hypopituitarism should be investigated in suspected patients with neurologic symptoms. Emergency medicine, internal medicine, and infectious diseases specialists should be aware of this complication to reduce mortality and morbidity.

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