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CASE REPORT

Hemorrhagic fever with renal syndrome accompanied by panhypopituitarism and central diabetes insipidus: a case report

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Abstract
Central diabetes insipidus (DI) was detected in a patient with hemorrhagic fever with renal syndrome (HFRS) who had been molecularly and serologically diagnosed with Hantaan virus infection. We recommend that clinicians differentiate central DI in HFRS patients with a persistent diuretic phase even when pituitary MRI findings are normal.

Keywords Hantaan virus · Viral hemorrhagic fevers · Diabetes insipidus · Hypopituitarism

Introduction

Hemorrhagic fever with renal syndrome (HFRS), caused by various hantaviruses in the Bunyaviridae family, is an infectious zoonotic disease transmitted by rodents and is widely prevalent in Asia and Europe. This acute hemorrhagic disease is characterized by renal failure, hemorrhage, thrombocytopenia, and shock and has five clinically progressive phases: febrile, hypotensive, oliguric, diuretic, and convalescent. Most cases show improvement without complications, but some may involve hemorrhage and congestion in the pituitary, right atrium, and renal medulla in the oliguric stage (Kim 2009; Lee et al. 1986). Autopsies conducted on the bodies of patients with acute HFRS revealed anterior pituitary hemorrhage and necrosis, and computed tomography (CT) scans performed after the convalescent stage detected pituitary atrophy (Suh et al. 1995). Most cases of hypopituitarism induced by HFRS involve the anterior pituitary, with only rare cases of posterior pituitary hormonal dysfunction (Lee et al. 1986). We report a case of panhypopituitarism and central diabetes insipidus (DI) developed in the convalescent stage in a patient with HFRS resulting from Hantaan virus infection, confirmed using polymerase chain reaction (PCR) and antibody tests.

Case report

A 54-year-old man presented to our hospital with fever, chills, and vomiting. He had been working on a paprika farm in Jangheung, Jeollanam-do, and cleaned the vinyl greenhouse 7 days previously. He purchased a non-steroidal anti-inflammatory drug from a local pharmacy to treat his fever, but his symptoms did not abate. He began to vomit 2 days before his visit to our hospital; at that time, he visited a neighborhood hospital where tests revealed an elevated white blood cell count (23,000/mm^3) and hypotension. He was transferred to our emergency department with suspected sepsis.

On presentation to the emergency department, the patient was fully conscious but looked sick. His blood pressure was 80/60 mmHg; pulse, 80 beats/min; respiratory rate, 20 breaths/min; and body temperature, 37.5 °C. Physical examination showed facial and neck flushing, mild facial edema, conjunctival injection, and oral petechiae. Chest auscultation confirmed normal heart and breathing sounds. He had mildly depressed bowel movement and generalized abdominal tenderness and bilateral severe tenderness of the costovertebral angles.

Peripheral blood testing showed a white blood cell count of 30,380/mm^3 (77.3% neutrophils); hemoglobin, 21.9 g/dL; hematocrit, 62.7%; and platelet count, 70,000/mm^3. Serological test results were blood urea nitrogen, 38.5 mg/dL; creatinine,

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3.23 mg/dL; aspartate amino transferase, 205 U/L; alanine amino transferase, 38 U/L; protein, 5.74 g/dL; albumin, 2.93 g/dL; sodium, 134 mEq/L; potassium, 4.1 mEq/L; and chloride, 103 mEq/L. Urine analysis showed a specific gravity of 1.015; microscopic red blood cells, 5–9/HPF; white blood cells, 1–4/HPF; and proteinuria, +++. The urine output was 400 mL/24 h, indicating oliguria. We considered the possibility of HFRS in the oliguric stage and requested a total immunofluorescent antibody assay (IFA) test at a commercial laboratory (Green Cross Corporation, Korea), with results of 1:40 for the Hantaan virus antibody test, which increased to 1:320, 5 days later. The in-house IFA test confirmed an elevation of IgG titers from 1:16 to 1:512 6 days later, while IgM titer remained at < 1:16. The titers were IgM < 1:16 and IgG 1:512, 1 month later (Lim et al. 2012).

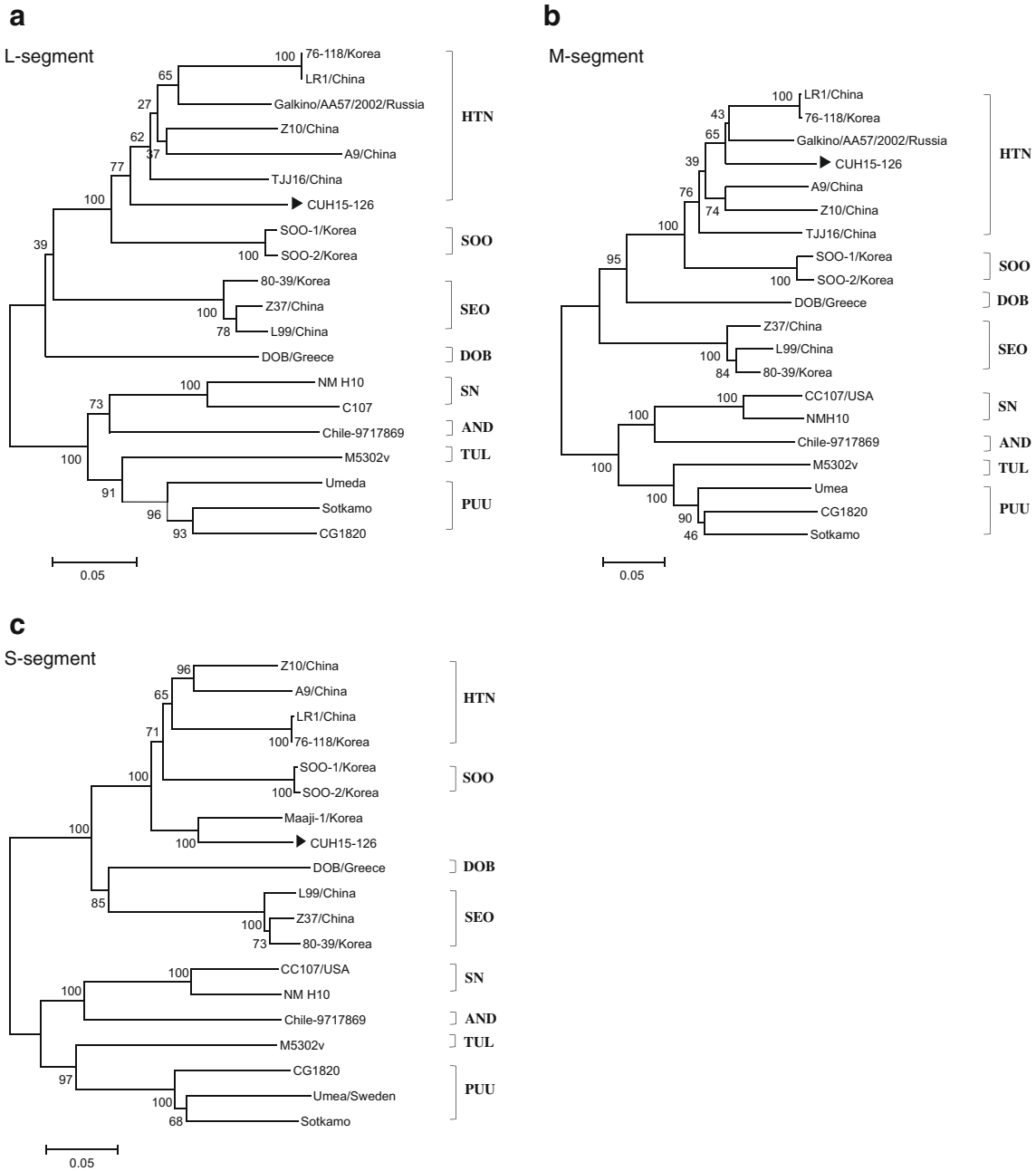

Fig. 1 Phylogenetic trees for hantaviruses based on the partial L-segment genome sequences (360 nucleotides, **a** GenBank accession no. of CUH15-126: MG663537), the partial M-segment genome sequences (350 nucleotides, **b** GenBank accession no. of CUH15-126: MG663538), and the partial S-segment genome sequences (650 nucleotides, **c** GenBank accession no. of CUH15-126: MG663539). The numbers at the nodes are bootstrap confidence levels for 1000 replicates. HTN, Hantaan virus; SEO, Seoul virus; SOO, Soochong virus; SN, Sin Nombre virus; PUU, Puumala virus; AND, Andes virus; TUL, Tula virus; DOB, Dobrava-Belgrade virus

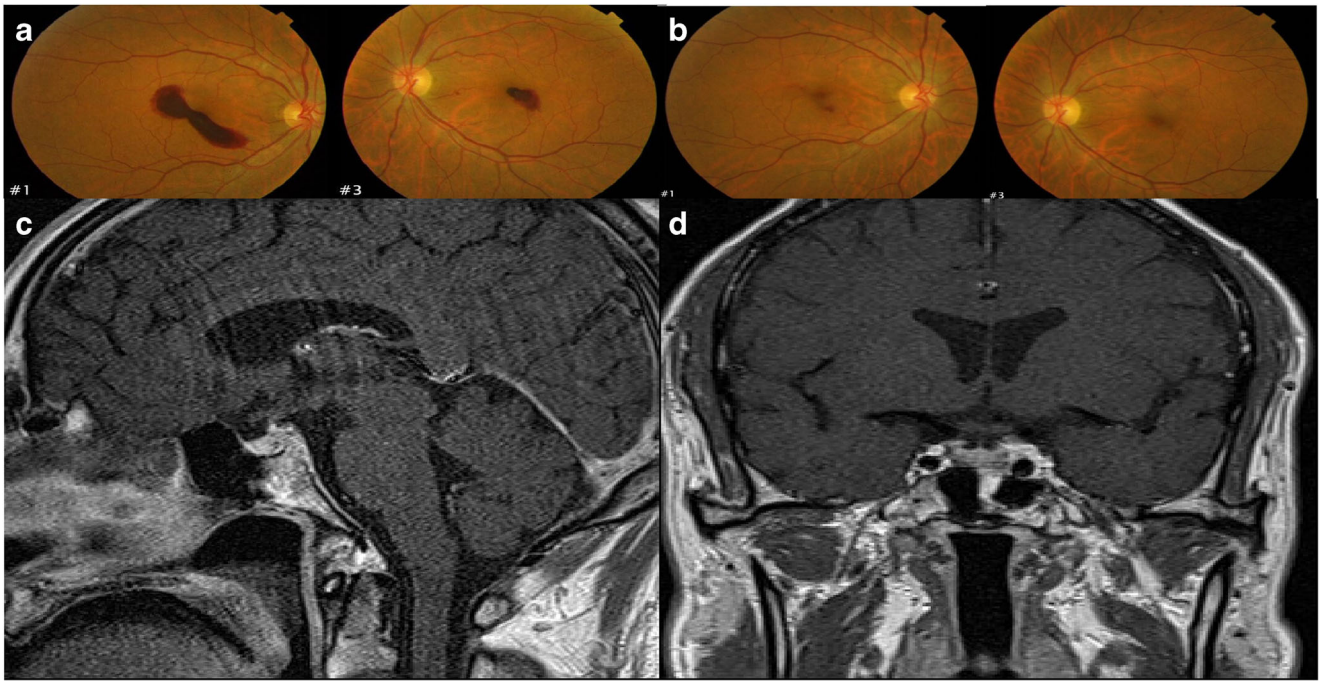

Fig. 2 **a** In the patient diagnosed with HFRS, fundoscopy showed bilateral macular hemorrhage. **b** After 3 months of conservative treatment, fundoscopy showed an improved state. Contrast-enhanced sagittal T1-weighted image (**c**) and contrast-enhanced coronal T1-weighted image (**d**) show the size (vertical height 6.5 mm), shape, and density of the normal pituitary gland

We obtained viral RNA from the patient's plasma using the Viral Gene-spin™ Viral DNA/RNA Extraction Kit (iNtRON Biotechnology, Korea). A nested reverse transcription PCR targeting the large (L: encodes viral RNA-dependent RNA polymerase) segment of genus *hantavirus* was performed with cDNA synthesized using Super Script™ VILO™ Master Mix (Invitrogen) (Klempa et al. 2006). Positive PCR products targeting L, M, and S segments of Hantaan virus were sequenced and then analyzed using CLUSTAL X, Tree Explorer, LaserGene Program (DNASTAR, Madison, WI) program. That sequences were submitted to NCBI GenBank (accession nos. MG663537, MG663538, MG663539).

A phylogenetic tree analysis was performed using L-segment targeted PCR (Baek et al. 2006) with an amplification of 360 bp (Fig. 1a). BLASTN showed 83.3% homology with Hantaan virus isolate TJJ16 and Galkino/AA57/2002 (accession nos. KU215675, AB620033), 82.5% with Hantaan virus strain Z10 (accession no. AF189155), and 79.4% for both Hantaan virus strains 76-118 and LR1 (accession nos. NC_005222, AF288292). The specimen was 79.7 and 78.9% homologous with Soochong virus strains SOO-1 and SOO-2 (accession nos. DQ056292, AY675354), respectively. A phylogenetic tree analysis using hantavirus M-segment targeted PCR with an amplification of 350 bp

Table 1 Results of the combined pituitary stimulation test

	After stimulation					Normal response
	Basal	30 min	60 min	90 min	120 min	
Glucose (mg/dL)	92	86	30	47	34	< 40 mg/dL or < 50% of baseline
TSH (μIU/mL)	2.5	1.8	3.0			Peak TSH > basal TSH + 5 μIU/mL
Prolactin (ng/mL)	16.5	16.5	18.7			Peak PRL > 300% of baseline
LH (mIU/mL)	0.31	0.55	0.65			Peak LH > basal LH + 10mIU/mL
FSH (mIU/mL)	2.0		2.35	2.23	2.81	Peak FSH > basal FSH + 2mIU/mL
hGH (ng/mL)	0.36		0.4	0.5	0.23	Peak GH > 200% of baseline
Cortisol (μg/dL)	1.3		1.5	4.0	5.6	Peak cortisol > 20 μg/dL or increased by 7 μg/dL
ACTH (pg/mL)	5.2	5.6	33.5	37.3	40.0	Response decision by cortisol response

TSH, thyroid-stimulating hormone; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone; *hGH*, human growth hormone; *ACTH*, adrenocorticotropic hormone

Table 2 Water deprivation test

	Urine osmolality (mOsm/kg)	Plasma osmolality (mOsm/kg)
6 AM	196	297
7 AM	185	
8 AM	221	304
9 AM	242	
10 AM	262	299
11 AM	250	
Vasopressin		
After 30 min	327	311
60 min	385	321

showed 88.6% homology with Hantaan virus isolate Lee (accession no. D00377) and 87.1% homology with Hantaan virus isolate Galkino/AA57/2002 (accession no. AB620032) (Fig. 1b). Moreover, 86.9, 86.6, 84, and 82% homologies were shown for Hantaan virus strain LR1, 76-118, A9, and TJJ16 (accession nos. AF288293, Y00386, AF035831, EU074672), respectively. The isolate was also 80.9 and 80% homologous with Soochong virus strains SOO-1 and SOO-2 (accession nos. AY675353, DQ056293), respectively. A phylogenetic tree analysis using hantavirus S-segment targeted PCR with an amplification of 650 bp (Fig. 1c) revealed a homology of 87.6% with Hantaan virus strain Maaji-1 (accession no. AF321094), 81.2% with Hantaan virus strain 76-118 (accession no. M14626), and 81.1, 80, and 80% with Hantaan virus strains LR1, Z10, and A9 (accession nos. AF288294, AF184987, and AF329390), respectively. The specimen was also 79.5 and 79.4% homologous with Soochong virus strains SOO-1 and SOO-2 (accession nos. AY675349, AY675350), respectively. Antibody tests for *Leptospira*, *Orientia tsutsugamushi* yielded negative results, and follow-up tests showed no elevation in antibody titers.

Plain chest and abdominal radiographs showed no abnormal findings. The patient showed reduced vision and bilateral conjunctival hemorrhage. Fundoscopy showed bilateral submacular hemorrhage, but visual field examination showed no abnormal findings (Fig. 2).

Despite initially presenting with oliguria, his urine output began to increase on the second day to reach a 24-h urine output of 5–10 L after fluid therapy and preservative treatment. The diuretic stage persisted for > 3 weeks, with a daily urine output of > 10 L. The patient experienced thirst and general weakness. Serum cortisol, thyroid, and pituitary hormonal tests and a water deprivation test were performed, revealing a luteinizing hormone (LH) level of 0.31 mIU/mL (normal range, 1.5 to 9.3); follicle-stimulating hormone (FSH), 2.0 mIU/mL (normal range, 1.4 to 18.1); human growth hormone, 0.36 ng/mL (normal range, 0 to 1.0); and cortisol, 1.3μg/dL (normal range, 51.8 to 470.7); FSH and hGH were lower in the normal range; other hormone levels were lower than normal. A combined pituitary stimulation test was performed to assess hypopituitarism more accurately. Luteinizing hormone-releasing hormone (LHRH) 100 μg + thyrotropin-releasing hormone (TRH) 400 μg + regular insulin (RI) 7 U were injected intravenously. After stimulation, hormone levels did not reach the threshold range. Therefore, panhypopituitarism was diagnosed (Table 1) (Dennis et al. 2015). The patient was diagnosed with panhypopituitarism, and prednisone and thyroid hormone were administered. In the results of a water deprivation test, the urine osmolality increased from 196 to 250 mOsm/kg. After water deprivation, aqueous vasopressin (5 U) was injected intravenously. Urine osmolality was elevated by > 50% compared with baseline levels (250 to 385 mOsm/kg); thus, the patient was diagnosed with complete central diabetes insipidus (DI) (Table 2) (Goldman and Schafer 2016). Brain MRI approximately 1 month after admission showed normal vertical height of the pituitary (6.5 mm) with no abnormal contrasts or atrophy (Fig. 2). Desmopressin was administered and his 24-h urine output dropped to 3 L, with improvement in the symptoms of thirst and polyuria. The patient showed

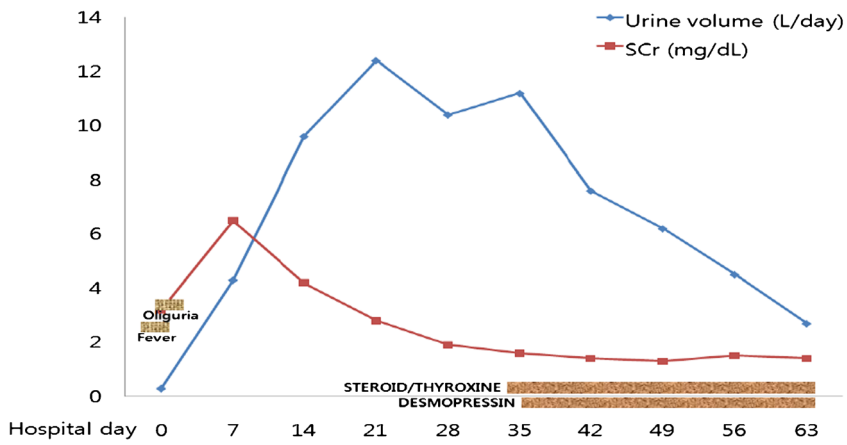

Fig. 3 Clinical course of the presented case. Urine output increased up to 12 L during the third week after admission and decreased to 3 L after the administration of desmopressin. SCr, serum creatinine

improvement with continued administration of prednisone, thyroid hormone, and desmopressin (Fig. 3).

Discussion

HFRS is an infectious zoonotic disease transmitted by rodents widely distributed in Asia and Europe. Most cases of HFRS in South Korea are caused by Hantaan virus and transmitted by *Apodemus agrarius* in rural areas. The risk of infection is heightened when working outdoors in areas inhabited by these rodents. Upon infection, symptoms such as fever and hemorrhage develop due to vasodilation and blood leakage, and the pathogenic virus infiltrates the vascular system, affecting a wide range of tissues and organs (Kim 2009; Lee et al. 1986). The heart, kidneys, and pituitary are affected, and the anterior pituitary is more affected than the posterior pituitary. The lesions are primarily ischemic injuries due to vasoconstriction caused by shock and hemorrhage, vasopermeability changes caused by virus-related mediators, and thrombosis caused by disseminated intravascular coagulation (Stojanovic et al. 2008). In most cases, 50–90% of the pituitary tissue is affected; clinical dysfunction may develop if > 75–80% of the pituitary is affected. A study investigating 60 HFRS patients found that 11 of the 60 patients (18%) deranged hormonal levels (Stojanovic et al. 2008; Chung et al. 1996). Another study of autopsies performed on HFRS patients confirmed that 72–76% of the patients had anterior pituitary necrosis and that most patients who died from HFRS showed necrosis (Hullinghorst and Steer 1953; Lukes 1954).

There is a recent study of pituitary hormone changes in nephropathia epidemica (NE), a mild form of HFRS caused by Puumala virus. The pituitary gland had been found to be affected in two of the 58 patients investigated in this study. This follow-up investigation did not reveal any obvious late-onset pituitary insufficiency cases (Terhi et al. 2016).

Radiologic diagnosis is performed using brain computed tomography scan and MRI, and approximately 70% of patients show abnormally low sellar density or an empty sella (Lee et al. 1986). The primary cause of central DI in HFRS patients is neural loss caused by an injury of the pituitary stalk rather than a direct injury of the posterior pituitary, resulting from the severe anterior pituitary damage causing the injured stalk to be replaced with fibrous connective tissue (Chung et al. 1996). Although cases of anterior pituitary hormonal dysfunction caused by HFRS are rather common, there are few data on the involvement of the posterior pituitary.

Clinicians should suspect panhypopituitarism and central DI in HFRS patients with clinical manifestations suggesting hypopituitarism or in HFRS patients displaying a prolonged diuretic phase despite improvement of other clinical symptoms, even if they have normal pituitary MRI findings, as our patient. Hypopituitarism is diagnosed using basal hormone and combined pituitary stimulation tests, and a failure of elevation of hormone levels above the standard levels even after stimulation indicates hypopituitarism (Lee et al. 1986). A water deprivation test can confirm central DI, through which clinicians should differentiate between central DI caused by hypopituitarism and nephrogenic DI (Chung et al. 1996).

Patients diagnosed with hypopituitarism and central DI based on these diagnostic methods must be treated with hormone replacement therapy. Clinicians should note that some patients with HFRS also have hormone abnormalities and perform appropriate assessments for suspected patients.

We describe a case in which central DI was confirmed in a patient with HFRS based on PCR and elevation of antibody titers. We stress the importance of differentiating central DI in HFRS patients who show a persistent diuretic phase after HFRS treatment even if they have normal pituitary MRI findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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