Dobrava Hantavirus Infection Complicated by Panhypopituitarism, Istanbul, Turkey, 2010

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We identify Dobrava-Belgrade virus infection in Turkey (from a strain related to hantavirus strains from nearby countries) in a patient who had severe symptoms leading to panhypopituitarism, but no known risk for hantavirus. Our findings emphasize the need for increased awareness of hantaviruses in the region and assessment of symptomatic persons without known risk factors for infection.

Hemorrhagic fever with renal syndrome (HFRS) is caused by infection with hantaviruses. Most patients with HFRS recover completely, but acute and chronic complications may develop. HFRS patients with severe lung involvement resembling hantavirus cardiopulmonary syndrome have been described (1). In addition, pituitary hemorrhage, followed by hypopituitarism, is a possible complication of HFRS. Involvement of the pituitary gland has been observed in some patients infected with Puumala virus, a hantavirus commonly found in western and central Europe (2–4).

We report on a patient who experienced shock, pulmonary failure, and panhypopituitarism as complications of HFRS. By testing for neutralizing antibodies and by amplification and molecular characterization of virus samples, we identified the causative pathogen as a strain of Dobrava-Belgrade virus (DOBV) that is closely related to a hantavirus strain typically carried by the yellow-necked field mouse (Apodemus flavicollis), strain DOBV-Af.

The Case-Patient

A 34-year-old man with fever (38°C), tender cervical lymph nodes, and symptoms of pharyngeal infection was admitted to a hospital in Istanbul, Turkey on February 3, 2010. His blood pressure was 120/70 mm Hg and heart rate was 96 beats/min. Laboratory findings included thrombocytopenia (63,000 platelets/mm³ [reference 130–450×10³ platelets/mm³]) and mild elevation of transaminase levels (alanine transaminase 95 IU/L [reference 10–40 IU/L]; Aspartate aminotransferase 99 IU/L [reference 15–40 IU/L]) (Table 1). Results of urinalysis, chest radiograph, and ultrasound of the abdomen were normal. Diarrhea developed during the first day of hospitalization, and conjunctival suffusion was observed on ocular examination. Ciprofloxacin was given to treat suspected salmonellosis at a dosage of 400 mg every 12 hours.

On day 2 of hospitalization, the patient became oliguric and hypotensive. He had persisting fever. His platelet count decreased to 20,000/mm³, and his serum creatinine level increased to 1.8 mg/dL (reference 0.7–1.2 mg/dL). Urinalysis results showed microscopic hematuria and proteinuria. Results of a transthoracic echocardiogram showed heart chambers of normal size, a left ventricular ejection fraction of 60%, and moderate pericardial effusion. The patient was transferred to the intensive care unit. Broad-spectrum antimicrobial drugs were initiated as treatment for suspected sepsis, and platelet and albumin transfusions were given as supportive therapy.

On day 3 of hospitalization, the patient experienced tachycardia, petechial lesions appeared on his extremities, and his platelet count dropped to 13,000/mm³. Results of a bone marrow aspiration showed proliferation of histiocytes and prominent hemophagocytosis. Intravenous methylprednisolone therapy (100 mg/day) was started. Septic shock developed in the patient, and inotropic therapy was initiated. On the same day, acute respiratory distress syndrome developed, and assisted ventilation was started. Results of a thoracic computerized tomographic scan showed focal infiltration on the upper zone of the left lung and minimal pleural effusion on the right lung. Results of abdominal computerized tomographic scan revealed ascites and multiple mesenteric lymphadenomegaly. On the basis of these clinical and laboratory findings, hantavirus infection was suspected. Blood samples were obtained for hantavirus testing, and oral ribavirin was added at an initial dose of 30 mg/kg, followed by 15 mg/kg every 6 hours for 4 days, then 7.5 mg/kg for 6 days. On the same day,
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Table 1. Hematologic and biochemical parameters of DOBV hantavirus patient, Istanbul, Turkey, 2010

| Laboratory test (reference range) | Day of hospitalization |
|----------------------------------|------------------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 15 | 20 | 71 |
| Leukocytes, × 10³ cells/mm³ (4.5–11) | 5.8 | 9.9 | 15.2 | 27.6 | 24 | 25 | 11.3 | 4.7 | 7.7 |
| Hemoglobin, g/dL (11.7–15.5) | 16 | 16.5 | 18 | 16 | 13.3 | 10.7 | 8.2 | 8.9 | 12.1 |
| Hematocrit, % (36–46) | 46.7 | 48 | 51.8 | 45.2 | 38.3 | 31.2 | 24.6 | 27 | 36.6 |
| Platelets, × 10³/mm³ (130–450) | 63 | 19 | 20 | 13 | 37 | 55 | 180 | 171 | 254 |
| ALT, U/L (10–40) | 95 | 92 | 58 | 67 | 157 | 539 | 79 | 60 | 20 |
| AST, U/L (15–40) | 99 | 117 | – | – | 497 | 2234 | 106 | 84 | 25 |
| BUN, mg/dL (4.67–23.3) | – | 16 | 23 | 30 | 41 | 41 | 129 | 74 | 19 |
| Creatinine, mg/dL (0.7–1.2) | – | 0.8 | 1.8 | 2.4 | 3.3 | 3.1 | 7.3 | 6.4 | 1.92 |
| aPTT, s (4–40) | – | 39 | 43 | – | 32.5 | 37.1 | 30.8 | – | – |
| PT, s (10–14) | – | 13.3 | 11.6 | – | 17.5 | 20 | 14.1 | – | – |
| Ferritin, ng/mL (15–200) | – | 5,304 | – | – | 14,036 | – | – | – | – |
| TSH, U/mL (0.4–4.2) | – | 1.71 | – | – | – | – | – | 2.83 | 0.92 |
| Free thyroxin, pmol/L (10.3–23.2) | – | – | – | – | – | – | – | 0.18 | 14.3 |
| Cortisol, µg/dL (6.2–19.4) | – | – | – | – | – | – | – | 45.0 | 0.98 |
| ACTH, µg/dL (0–19.5) | – | – | – | – | – | – | – | 3.02 | 6.8 |
| ADH, pg/mL (0.8–4.5) | – | – | – | – | – | – | – | 2.2 | – |
| Total testosterone, ng/mL (2.8–8.0) | – | – | – | – | – | – | – | <0.025 | 1.9 |
| LH, mIU/mL (1.7–8.6) | – | – | – | – | – | – | – | <0.1 | – |
| FSH, mIU/mL (1.5–12.4) | – | – | – | – | – | – | – | 0.66 | – |
| Prolactin, mIU/mL (4.6–21.4) | – | – | – | – | – | – | – | 10.05 | – |
| Somatomedin-C/IGF-1, ng/mL (115–307) | – | – | – | – | – | – | – | 0.18 | 14.3 |
| Hemoglobin, g/dL (11.7–15.5) | 16 | 16.5 | 18 | 16 | 13.3 | 10.7 | 8.2 | 8.9 | 12.1 |
| Platelets, × 10³/mm³ (130–450) | 63 | 19 | 20 | 13 | 37 | 55 | 180 | 171 | 254 |
| ALT, U/L (10–40) | 95 | 92 | 58 | 67 | 157 | 539 | 79 | 60 | 20 |
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| BUN, mg/dL (4.67–23.3) | – | 16 | 23 | 30 | 41 | 41 | 129 | 74 | 19 |
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| Ferritin, ng/mL (15–200) | – | 5,304 | – | – | 14,036 | – | – | – | – |
| TSH, U/mL (0.4–4.2) | – | 1.71 | – | – | – | – | – | 2.83 | 0.92 |
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| Prolactin, mIU/mL (4.6–21.4) | – | – | – | – | – | – | – | 10.05 | – |
| Somatomedin-C/IGF-1, ng/mL (115–307) | – | – | – | – | – | – | – | <25 | – |

| *DOBV, Dobrava-Belgrade virus; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; aPTT, activated partial thromboplastin time; PT, prothrombin time; TSH, thyroid stimulating hormone; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; IGF, insulin-like growth factor.

Table 2. Characterization of DOBV hantavirus in a patient’s serum by focus reduction neutralization tests, Istanbul, Turkey, 2010

| Day of hospitalization | Focus reduction neutralization test endpoint titer |
|-----------------------|-----------------------------------------------|
| Puumala hantavirus    | Hantaan virus                                 |
| 5                     | <1:40                                         | <1:40                                      |
| 26                    | <1:40                                         | <1:40                                      |

| DOBV-Aa (strain SK)   | DOBV-Af (strain Slo) |
|-----------------------|----------------------|
| 1:640                 | 1:1,280              |
| 1:160                 | 1:320                |

*DOBV, Dobrava-Belgrade virus; Aa, Apodemus agrarius; Af, Apodemus flavicollis; SK, strain Slovakia; Slo, strain Slovenia.
Conclusions

The general symptoms and results of the serologic tests and molecular analyses for this patient were consistent with a hantavirus infection. After the acute phase of the illness, characterized by renal and pulmonary failure, panhypopituitarism developed in the patient. Pituitary hemorrhage and atrophy were observed on the magnetic resonance image. Case reports have documented that pituitary hemorrhage followed by panhypopituitarism may complicate HFRS (2–4), and Puumala virus was reported as the causative agent in most of these cases. In addition, hormonal deficiencies have been shown to be common features of Puumala virus infections, and chronic hormonal deficits develop in some patients (5). Our findings demonstrate that development of hypopituitarism can also be associated with infection by DOBV. Since the patient does not belong to any groups that have high exposure to hantaviruses (such as farmers, forest workers, and military recruits) and did not report any travel in hantavirus-endemic areas, the source of infection remains unclear.

In contrast to what is known about hantavirus presence in other Balkan states, little is known about the distribution, diversity, or host range of hantaviruses in Turkey (6). In 2009, a hantavirus outbreak occurred in Turkey; 3 of the 5 infected persons died (7). Serologic assays have been used to detect DOBV infection in patients in Turkey, but focus reduction neutralization tests have not been used for serotyping. DOBV RNA was found only in 1 urine sample from a hantavirus-infected patient from Turkey; however, sequence data were not provided (8). Prevalence studies of rodents collected in Turkey revealed 6% seropositivity to Puumala virus in Microtus voles and no appearance of hantavirus antibodies in the Apodemus species of rodents (9). Focus reduction neutralization testing and virus sequencing confirmed that the patient in our study was infected with DOBV-Af. This strain is associated with A. flavicollis field mice and yet has not been reported in animals in Turkey (see 10,11 for the molecular classification of Apodemus spp.–associated DOBV virus lineages).

This case should alert physicians that hantavirus infection should be considered in the differential diagnosis of patients who have high fever and thrombocytopenia, including those without known risk factors for hantavirus infection. The general symptoms and results of the serologic tests and molecular analyses for this patient were consistent with a hantavirus infection. After the acute phase of the illness, characterized by renal and pulmonary failure, panhypopituitarism developed in the patient. Pituitary hemorrhage and atrophy were observed on the magnetic resonance image. Case reports have documented that pituitary hemorrhage followed by panhypopituitarism may complicate HFRS (2–4), and Puumala virus was reported as the causative agent in most of these cases. In addition, hormonal deficiencies have been shown to be common features of Puumala virus infections, and chronic hormonal deficits develop in some patients (5). Our findings demonstrate that development of hypopituitarism can also be associated with infection by DOBV. Since the patient does not belong to any groups that have high exposure to hantaviruses (such as farmers, forest workers, and military recruits) and did not report any travel in hantavirus-endemic areas, the source of infection remains unclear.

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exposure. Since severe hormonal deficiencies are life-threatening, neuroendocrinologic complications should be taken into account and the endocrine status should be investigated to prevent panhypopituitarism even after recovery from HFRS.

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CDC’s Travelers’ Health Branch has created this online course for healthcare providers who want to learn more about yellow fever disease and yellow fever vaccine.

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• Understand yellow fever history and epidemiology
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• Identify the precautions and contraindications to yellow fever vaccination
• Recognize the common and rare adverse events associated with yellow fever vaccination
• Gain proficiency in conducting a thorough pre-travel consultation
• Learn best practices for yellow fever vaccine providers and clinics

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