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REVIEW ARTICLE

Hantavirus Infection in Turkey

Gülay Okay

Travel Health Service, Republic Of Turkey Ministry Of Health Directorate General Of Health For Border And Coastal Areas, Istanbul, Turkey

ABSTRACT

The Hantaviruses within the *Bunyaviridia* family carried by rodents cause two different diseases in humans: Hemorrhagic Fever with renal syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS). It is transmitted through contact with the secretion of infected rodents or through the inhalation of aerosols containing the virus. In different parts of the world, various virus subtypes cause the disease. In HPS, mostly Sin Nombre, Andes, Laguna, Negra and New York types are causative agents, whereas in HFRS the agents are Dobrava, Puumala, Hantaan, Saaremaa and Seoul. It is more frequently observed in forest areas receiving heavy rain and having a large rodent population. While HPS is seen in America, HFRS is mostly seen in Asia and Europe. The number of Hantavirus infections have been on the rise in the world day by day. Clinic cases associated with Hantavirus known to exist by seroepidemiological trials conducted in Turkey were defined for the first time in 2009 with an outbreak occurred in the north-west region of the country. The number of cases reported so far has reached 28. Here, it is aimed to review the Hantavirus cases occurred in Turkey up to the present and increase awareness about the disease. *J Microbiol Infect Dis 2014; Special Issue 1: S50-S53*

Key words: Hemorrhagic Fever with renal syndrome, HFRS, Hantavirus Pulmonary Syndrome, HPS, Emerging infectious diseases, Turkey

Türkiye'de Hantavirüs Enfeksiyonları

ÖZET

Kemirgenler tarafından taşınan Bunyaviridae ailesinde yer alan, Hantavirüsler, insanda iki farklı klinik tabloya neden olur: "Renal Sendromlu Hemorajik Ateş" (HFRS) ve "Hantavirüs Pulmoner Sendrom" (HPS). Enfekte kemirgenin salgıları ile temasla veya virüs içeren aerosollerin solunum yolu ile alınması ile bulaşır. Dünyanın farklı bölgelerinde farklı virüs alt tipleri hastalığa neden olur. HPS'de en sık SinNombre, Andes, Laguna, Negra ve New York türleri etkendir. HFRS'de Dobrava, Puumala, Hantaan, Saaremaa ve Seoul türleri neden olur. Bolca yağış alan ve büyük rodent popülasyonuna sahip ormanlık bölgelerde daha sık görülmektedir. HPS Amerika'da HFRS ise Asya ve Avrupa'da daha sık görülmektedir. Dünyada Hantavirüs enfeksiyonlarının sayısı her geçen gün artmaktadır. Türkiye'de yapılan seroepidemiyolojik çalışmalar ile varlığı bilinen Hantavirüs'ebağlı klinik olgular ilk defa 2009 yılında ülkenin kuzey-batı bölgesinde meydana gelen salgınla tespit edilmiştir. Günümüze kadar bildirilen olgu sayısı 28'e ulaşmıştır. Burada Türkiye'de bugüne kadar görülen Hantavirus olguları gözden geçirilerek hastalıkla ilgili farkındalığın arttırılması amaçlanmıştır.

Anahtar kelimeler: Renal Sendromlu Hemorajik Ateş, HFRS, Hantavirus kardiyopulmoner sendrom, Yeniden önem kazanan enfeksiyon hastalıkları, Türkiye

INTRODUCTION

Hantaviruses are enveloped RNA viruses each type of which is carried by specific rodents and which take place in Bunyaviridae family. They lead to asymptomatic and persistent infections in rodents causing life-long spread of the virus. It is transmitted to people through direct contact with an infected rodent's secretion or through aerosols containing virus. Depending on the physical distribution of the host, different virus types cause the disease in different geographies.[1,2]

Hantaviruses cause two clinical conditions known as Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS) in humans.[2,3] These occur in different regions of the world with different virus subtypes. HPS is

Correspondence: Dr. Gülay Okay, Hudut ve Sahiller Sağlık Genel Müdürlüğü, Sağlık Hizmetleri Daire Başkanlığı, İstanbul, Turkey Email: gulay.okay@hotmail.com
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mainly seen in the Americans and Sin Nombre, Andes, Laguna Negra and New York types are the most causative ones. HFRS is the disease type that occurs mostly in Europe and Asia and is caused by Dobrova, Puumala, Hantaan, Saaremaa and Seoul types. Puumala which is carried by bank vole is the type that is mostly seen in Europe. Hantavirus infections occur more frequently in forestry areas receiving plenty of rain and having great rodent population. Rodent population increase in living spaces, getting into buildings that are rarely used or that have been closed for a long time or cleaning such buildings are important risk factors in terms of disease progress.[3,4,5]

Symptoms resembling to HFRS disease were first described in Japanese soldiers affected by the disease in 1930s. Then, the disease was noticed among 3200 American soldiers during Korean War in 1951. In North America, where it was known that there had been various Hantaviruses before, epidemic was defined in humans by the first outbreak occurred in 1933. In the world, the prevalence of hantavirus infections increases every passing day and in many countries, this has been classified as endemic infection. Every year 40.000 – 100.000 people are affected by HFRS disease around the world. In Europe, more than 100.000 HFRS diagnoses are made every year and the number of cases increases gradually. It is not exactly known whether this situation arises from health care personnel who recognize the disease better now or from environmental factors such as climate change or from both.[2,3,4]

The existence of hantaviruses in Turkey was first identified in 2004 during a study on rodents. In this study, the existence of hantaviruses in 330 rodents collected from western and north-eastern regions of the country was shown through immunofluorescence assays (IFA) method.6 Other seroepidemiological studies that were carried out also support the existence of hantavirus.[7,8,9] In another important seroprevalence study performed on 306 serum samples taken from healthy people, Dobrava, Puumala and Saaremaa subtypes were also identified and 5.2% overall prevalence was seen.9 This data show that Hantavirus is circulating in the area.

In Turkey, the clinical cases of hantaviruses, the existence of which had been known for a while, were first identified in 2009, during an outbreak occurred in the north-western region of the country. In this outbreak during which 12 confirmed cases were seen between January and December, Puumala subtype was identified.9 After this outbreak, the number of cases reported from different cities of the country until today has reached up to 28[9,10,11,12,13,14,15,16,17,18,19] (Table 1, Figure 1). 25 of these cases were males and 3 females, and their ages range between 11 and 78. In 12 of them, there is a risk factor (such as being a farmer, living in a house with a garden, working in a less occupied building) 4 of the cases ended up with death.

Table 1. Number of cases by years and subtypes

Year seen	Case number	Hantavirus subtype and number
2009[9,10,18]	17	Puumala(12), Dobrava (3), ?(2)
2010[14,16,17]	4	Dobrava (2), ?(2)
2011[13]	1	Dobrava (1)
2012[11,12,15]	4	Dobrava(3), ?(1)
2013[19]	2	Puumala (1), Dobrava (1)
Total	28	Puumala (13), Dobrava (10) ? (5)

Figure 1. Cities with Hantavirus infection in Turkey and numbers

PATHOGENESIS

It is thought that in the pathogenesis of the disease, rather than direct cytopathic effect, immune response mechanisms are more effective. After the virus is taken through the respiratory tract, it reproduces in the localized lymph nodes and settles in vascular endotelin of lungs, heart, kidneys and lymphoid organs through viremia followed by a secondary viremia. After transmission to the target organs, immune system activates and cytokines (TNF-alfa, IL-1, IL-6) are released by macrophages and inflammatory response is stimulated. As a result of this vascular permeability increases and there is leakage of fluid outside the veins leading to hypotension and shock clinic. Atypical T lymphocytes trigger capillary leak during the disease.[2,20]

CD8+T cells, serum levels of which are higher when compared with other viral infections, cause lysis of cells infected with hantavirus. Therefore, tissue damage occurs more in people with high viremia and this causes the disease to progress slower. Especially at the beginning of the disease, people with high viremia are slowly progressive. In HFRS cases, renal edema and fluid leakage to the retroperitoneal space, perirenal hemorrhage and tubular degeneration and inflammation occur.[2,20]

CLINICAL FEATURES

HPS mostly seen in the Americans begins with fever, malaise, headache, muscle pain, dizziness, chill and gastrointestinal symptoms in its early stage. In advancing period, it progresses with cough and shortness of breath due to pulmonary edema and hypoxia, tachypnea, tachycardia and with cardiorespiratory involvement in which symptoms and findings of hypotension are seen. Mortality rate reaches up to % 50s in HPS patients.[2,4]

In HFRS disease, after the incubation period, sudden onset of fever, headache, severe abdominal pain, nausea and vomiting occur. In 3rd and 4th days of the illness, subconjunctival hemorrhage, palatal and truncal petechia may develop. Faces of great majority of patients turn red like sunburn. In slowly progressive cases, in addition to these symptoms, hemorrhagic symptoms and renal disfunction also occur. Relative bradycardia, hypotension in almost half of patients and shock in a few of patients are also other symptoms. In about 1% of patients, seizure and focal neurologic symptoms develop. After the incubation period, although they do not typically separate from each other totally, febrile, hypotensive, oliguric, polyuric and convalescent phases alternate with each other in HFRS clinic.[2,4,5,19,21] Mortality rate changes between 1% and 15%.[4]

In hantavirus infections, prognosis is identified by many factors together. These factors are; type of virus, genetic factors, demographic properties, adequacy of humoral immune response, clinical findings and laboratory findings. Mortality rates change according to the infections developing with hantavirus subtypes. For instance, while Puumala progresses with a low mortality rate like 1%, Dobrava's rate reaches up to 15%. Although the disease occurs mostly in men, mortality rate is higher in women. It was notified that advanced age affects mortality negatively. Mortality increases in patients in whom hemorrhage in the central nervous system, sepsis, secondary infection and disseminated intravascular coagulation (DIC) develop.[20,21] In the study in which clinical and laboratory fatality foresight factors were assessed in 22 hantavirus patient in Turkey, it was identified that in 31.8% of patients, there were hemorrhage findings and blood and blood products transfusion were applied to them.[5] In 31.8% of patients, DIC developed and mortality rate was identified to be 22.7%.[5]

LABORATORY FINDING

In the blood analyses of the patient, a decrease in the serum albumin levels and an increase in the hematocrit levels showing a leakage in the circulatory system; an increase in the white blood cell count accompanied by a left shift and a decrease in the thrombocytes count are seen. In severely progressed patients, mostly in HFRS patients, DIC develops. An increase in proteinuria, transaminases in a medium level, creatine phosphokinases (CPK), amylase and creatinine are reported. The level of thrombocytopenia is effective on the mortality level. Other than this, in the first application of the patient, high level of white blood cell (WBC), blood urea nitrogen (BUN), CPK, prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR (International normalized ratio) increase the mortality rate.[4,5,10] In Turkish patients with a fatal progression, the levels of WBC, BUN, CPK, PT, aPTT, D-dimer and INR values were found higher and the platelet levels lower.[5]

In the hypotensive phase, hematocrit increases and leukocytosis and thrombocytopenia develop. Albuminuria, hematuria are usually seen between the 2nd and 5th days of the disease. In the phase of diuresis, electrolyte anomalies are frequent. In

HFRS patients, death usually happens due to electrolyte imbalance, bleeding, or secondary infections during the diuresis phase.[21]

TREATMENT

There isn't any specific treatment for Hantavirus infection, so the mainstream treatment is supportive in which the perfusion is made in tissues. Patients should be managed in an intensive care unit where they can be followed in terms of bleeding, blood and tissue oxygenation, liquid and electrolyte balance, and blood pressure. Broad-spectrum antibiotics should be started until a diagnosis is made. Due to the risk of potential liquid leakage, intravenous liquid should be administered carefully. By carefully monitoring the diuresis, kidney functions of the patient, liquid and electrolyte balance should be maintained. There is usually a need for one or two hemodialysis sessions during the following-up of the patient. Especially in HPS cases, respiratory support may be needed. When thrombocytopenia comes to critical levels, thrombocyte replacement should be made.4 While it has not been shown that the use of intravenous Ribavirin in HPS patients is effective, it has been shown to decrease the fatality rate to a limited extend in HFRS patients.[22,23]

REFERENCES

1. Stock I. Hantavirus infections; Med. Monatsschr Pharm, 2008 Apr;31(4):127-36
2. Lisa A. Beltz. A Guide to Diseaes, Causative Agents, and surveillance. Emerg Infect Dis 2011; 431-450
3. Vaheri A, Henttonen H, Voutilainen L, Mustonen J, Sironen T, Vapalahti O.; Hantavirus infections in Europe and their impact on public health, Rev. Medical Vir. 2013;23(1):35-49
4. http://www.cdc.gov/hantavirus/
5. Uğur K, Yılmaz G, Volkan S, Sökel S, Kaya S, Köksal İ, Evaluation of clinical and laboratory predictors of fatality in patients with Hantavirus infection; . J Microbiol Infect Dis, 2012;2 (4): 155-159
6. Laakkonen J, Kallio-Kokko H, Oktem MA, et al. Serological survey for viral pathogens in Turkish rodents. J Wildl Dis 2006; 42(3): 672-6.
7. Oktem MA. Hantavirus infections and tick-borne encephalitis virus infections. ANKEM 2009;23(Suppl 2):245-8.
8. Kavukcu S, Turkmen M, Sahman S, Soylu A, Camsan T. What is the risk of nephropathy associated with Hantavirus in Aegean region. Turk Neph Dial Transpl 1997;3-4:131-5.
9. Ertek M, Buzgan T. An outbreak caused by hantavirus in the Black Sea region of Turkey, January-May 2009. Euro Surveill 2009; 14(20).pii:19214
10. Kaya S, Yılmaz G, Erensoy S, Yağçı Çağlayık D, Uyar Y, Köksal I. Hantavirus infection: two case reports from a province in the Eastern Black Sea Region, Turkey. MikrobiyolBul 2010; 44(3): 479-87.
11. Çakır D, Çelebi S, Korukluoğlu G, Bozdemir ŞE, Çetin BŞ, Hacımustafaoğlu M. Haemorrhagic Fever with Renal Syndrome by Hantavirus. Ankem Derg 2012; 26(4): 198-202.
12. Atalay YO, Dere K, Şen H, Küçükodacı Z, Önem Y, Özkan S. HantaviralHaemorrhagic Fever with Renal Syndrome: A case report and review. Yoğun Bakım Derg 2012; 10(4): 210-6.
13. Öncül A, Koçulu S, Çağlayık DY, Uyar Y. Hantavirus infection with a mild course in a patient from Giresun province: A case report. Turk Hij Den BiyolDerg 2011; 68(4): 209-14.
14. Sarıgüzel N, Hofmann J, Canpolat AT, et al. Dobrava hantavirus infection complicated by panhypopituitarism, Istanbul, Turkey, 2010. Emerg Infect Dis 2012; 18(7): 1180-3.
15. Sünbül M, Yılmaz H, Çetinkaya H, et al. Two cases of hantavirus infection in Crimean-Congo hemorrhagic fever endemic region. J Microbiol Infect Dis 2012; 2(3): 117-20.
16. Oncul O, Atalay Y, Onem Y, Turhan V, Acar A, Uyar Y. Hantavirus infection in Istanbul, Turkey. Emerg Infect Dis 2011; 17(2): 303-4.
17. Öngürü P, Yılmaz S, Akıncı E, et al. Hemorrhagic Fever with renal syndrome: Two case reports. Turk Hij Den BiyolDerg 2011; 68(1): 35-9.
18. Gözel MG, Engin A, Elaldı N, Bakır M, Dökmetaş İ, Uyar Y. First cases of hemorrhagic fever with renal syndrome from the Middle Anatolia Region of Turkey and the first case of Hantavirus and Crimean-Congo hemorrhagic fever virus coinfection in a patient. Turk Klin J Med Sci 2013; 33(1): 224-8.
19. Özkan O, Tükek T, Yıldız E, Velioğlu EA, Gürsu M, Öztürk S. Hantavirus infections and renal manifestations: case report and update. Turk Neph Dial Transpl 2013; 22(1): 129-32.
20. Kaya S, Prognostic Factors in Hantavirus Infections. Mikrobiyol Bul. 2014; 48(1): 179-187
21. http://www.merckmanuals.com/professional/infectious_diseases/arboviridae_arenaviridae_and_filoviridae/hantavirus_infection.html
22. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective, double blind, concurrent, placebo-controlled clinicaltrial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 1991; 164(6):1119-27.
23. Rusnak JM, Byrne WR, Chung KN, et al. Experience with intravenous ribavirin in the treatment of hemorrhagicfever with renal syndrome in Korea. Antiviral Res 2009; 81(1): 68-76.