Hantavirus Enfeksiyonu Tanı Zorlukları

Dr. Ahmet Melih Şahin

Giresun Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

- Viral kanamalı ateş etkenidir

- Bunyaviridea ailesinden zarflı RNA virusudur
- Grup C bildirimi zorunlu hastalık

- Dezenfektanlara duyarlı

- Günümüze kadar sayısı artmakla birlikte 20’den fazla insanlarda patojen hantavirus tipi var

- Her hantavirüs tipi o tipe özgün kemirici tarafından taşınır.

TARİHÇE

- Bin yıl önceki Çin metinlerinde ateş ve renal yetmezlikle seyreden hastalık
- 1900-1950 yılları arasında Çin, Kore ve İskandinav ülkelerinde ‘siper nefriti’ ‘hemorajik nefrozonefrit’ ‘nepheropatia epidemica’ gibi isimlerle anılan salgın hastalık tabloları

- 1950-1953 kore savaşı sırasında 3000’den fazla Amerikalı ve Koreli askeri etkileyen ‘Kore Kanamalı Ateşi’
- 1976-1978 yılları arasında Kore’de Lee kemiricilerden hantavirusu izole etmiş
- Sonraki yıllarda birçok ülkede farklı hantavirus tipleri izole edilmiş.

- 1983 yılında DSÖ tarafından ‘renal sendromla seyreden kanamalı ateş’(RSKA)
- 1993 yılında ABD‘de Navajo yerlilerinde akut solunum yetmezliği ve yüksek fatalite hızı ile karakterize salgın ‘hantavirus pulmoner sendrom’ (HPS)
- 1996 yılında Arjantin’ de Andes virüs…

Johnson KM. The discovery of hantaan virus: comparative biology and serendipity in a world at war. J Infect Dis. 2004; 190(9): 1708-10.
Schmaljohn C. Vaccines for hantaviruses. Vaccine. 2009; 27(Suppl. 4): D61-4.
Simpson SQ, Spikes L, Patel S, Faruqi I. Hantavirus pulmonary syndrome. Infect Dis Clin North Am. 2010; 24(1): 159-73
Çelebi G Klimik Dergisi 2011; 24(3): 139-49

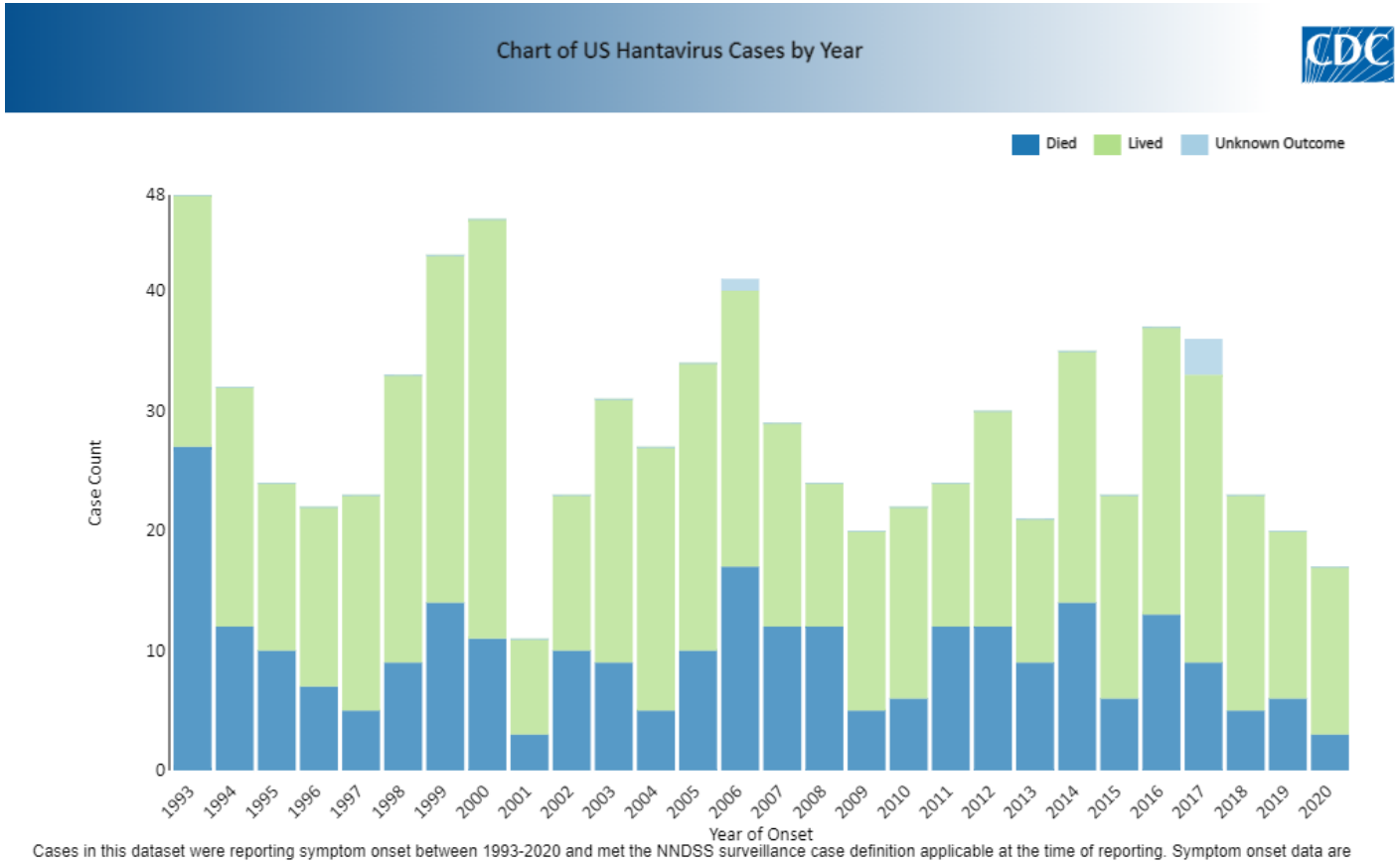
- 1993 GATA ‘dan 130 kişide…
- Ülkemizde ilk çalışma 2004 yılında kemiriciler üzerinde yapılmış , PUUV alt tipinin varlığı tespit edilmiştir
- 2009 yılında Zonguldak ve Bartın bölgesinden vakaların gelmesiyle bir dizi seroepidemiyolojik çalışmalar başlatılmış

- 2010 yılında Giresun’da 215 haneye gidilerek 15-84 yaş arası 626 kişiden kan örneği alınmış: 20’sinde Immununblot test pozitif(seroprevelans 3,2)

Dereli %13,9, Şebinkarahisar %10 Tirebolu %5,3, Espiye %5, merkez %2,5
Betonarme evde yaşayanlarda prevalans %2,2 iken ahşap ve kerpiç evlerde yaşayanlarda %9,5 (p:0,001)
Tuvaleti kanalizasyona bağlı evlerde yaşayanlarda prevalans %1,3 bağlı olmayanlarda %4,3 (p:0,003)
%55 kadın, %80’i 35 yaş üstü
%75’i bahçeli evde yaşamakta
%85’inin evinde gıda ve eşyaların depolandığı ek bir yapı bulunmaktadır
DOBV, PUUV, Saaremaa alt tipleri tespit edilmiş

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
Gozalan A, Kalaycıoğlu H, Uyar Y, et al. Human puumala and dobrava hantavirus infections in the Black Sea region of Turkey: a cross-sectional study. Vector Borne Zoonotic Dis 2013; 13(2): 111-8.

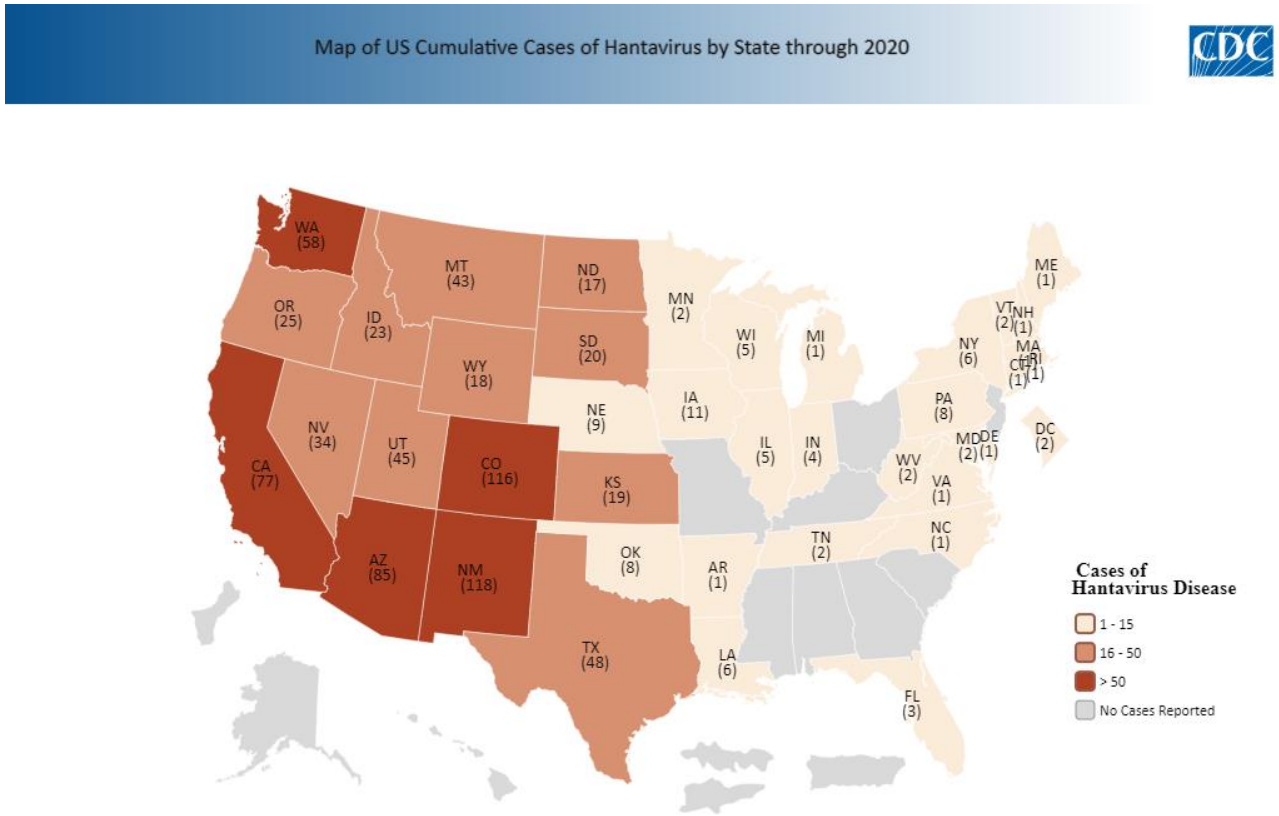
1993-2020 arası 833 vaka



Reporting of annual case information is delayed due to the COVID-19 pandemic.

AMERİKA KITASI

1993-2020 arası 833 vaka



All cases were confirmed between 1993-2020 and met the NNDSS case definition applicable at the time of reporting. Included in the sum total are 31 historical cases that occurred prior to 1993, but were confirmed retrospectively. Five cases had presumed exposure outside the United States.

AVRUPA KITASI

Table 1. Distribution of hantavirus infection cases and rates per 100 000 population by country and year, EU/EEA, 2016–2020

Country	2016		2017		2018		2019		2020	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Austria	30	0.3	90	1.0	24	0.3	276	3.1	30	0.3
Belgium	38	0.3	123	1.1	85	0.7	57	0.5	9	0.1
Bulgaria	10	0.1	8	0.1	7	0.1	6	0.1	1	0.0
Croatia	31	0.7	389	9.4	18	0.4	191	4.7	17	0.4
Cyprus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Czechia	10	0.1	17	0.2	4	0.0	15	0.1	5	0.0
Denmark	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Estonia	11	0.8	26	2.0	15	1.1	26	2.0	17	1.3
Finland ★	1663	30.3	1246	22.6	999	18.1	1256	22.8	1164	21.1
France	58	0.1	236	0.4	55	0.1	131	0.2	26	0.0
Germany ★	282	0.3	1731	2.1	235	0.3	1535	1.8	229	0.3
Greece	1	0.0	2	0.0	3	0.0	1	0.0	1	0.0
Hungary	7	0.1	16	0.2	6	0.1	13	0.1	4	0.0
Iceland	ND	NR	ND	NR	0	0.0	0	0.0	0	0.0
Ireland	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Italy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Latvia	8	0.4	4	0.2	3	0.2	5	0.3	3	0.2
Liechtenstein	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Lithuania	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Luxembourg	1	0.2	15	2.5	0	0.0	8	1.3	0	0.0
Malta	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Netherlands	2	0.0	6	0.0	1	0.0	0	0.0	0	0.0
Norway	10	0.2	26	0.5	21	0.4	11	0.2	12	0.2
Poland	8	0.0	14	0.0	11	0.0	9	0.0	3	0.0
Portugal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Romania	0	0.0	12	0.1	1	0.0	4	0.0	1	0.0
Slovakia	6	0.1	53	1.0	88	1.6	94	1.7	50	0.9
Slovenia	12	0.6	76	3.7	12	0.6	252	12.1	14	0.7
Spain	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0
Sweden	92	0.9	158	1.6	243	2.4	155	1.5	61	0.6
UK	ND	NR	ND	NR	ND	NR	3	0.0	ND	NR
EU-EEA	**2280**	**0.5**	**4249**	**1.0**	**1831**	**0.4**	**4048**	**0.8**	**1647**	**0.4**

Source: country reports.
ND: no data reported

2020'de Avrupa'dan bildirilen vaka sayısı 1647(100000 de 0,4)

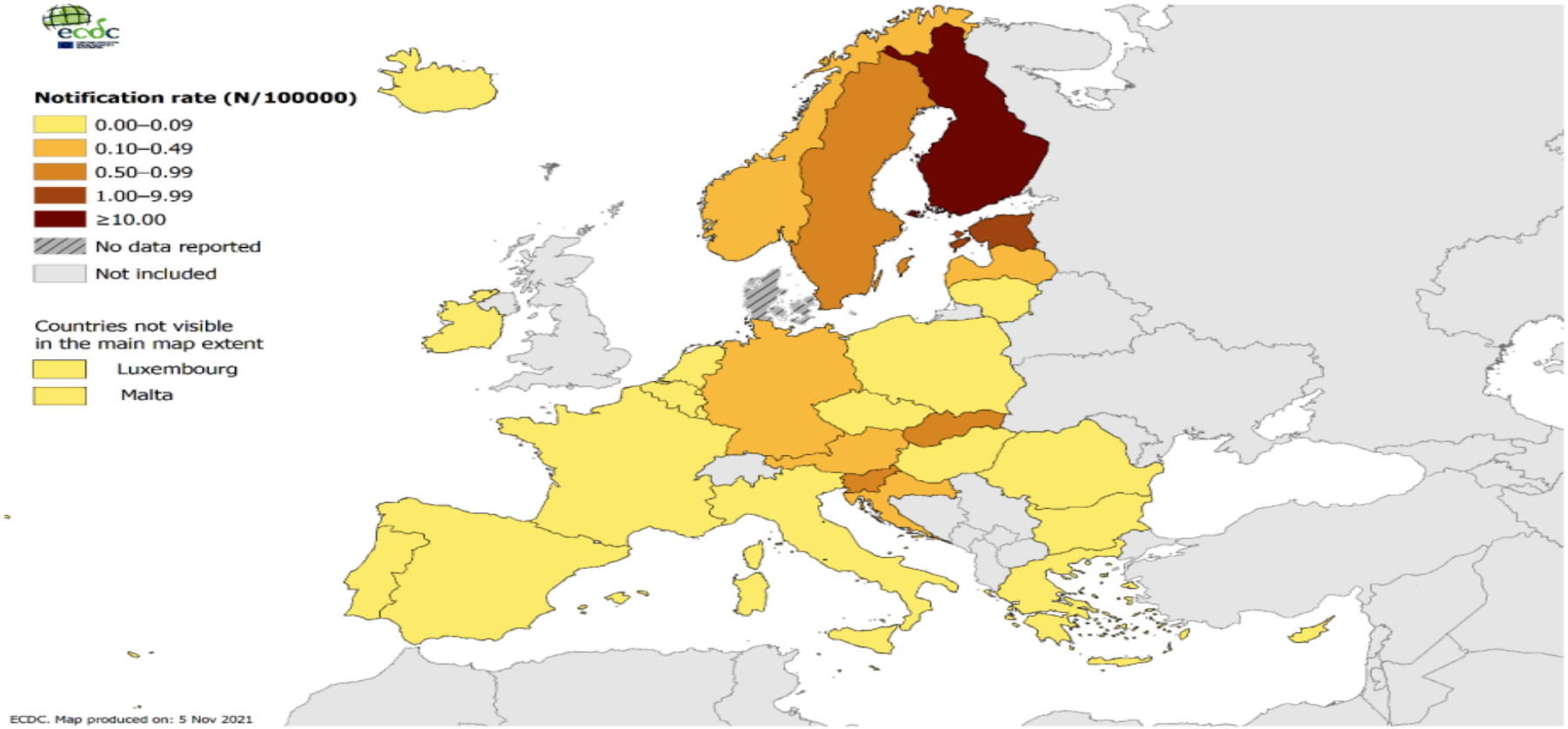
%98'i Puumala virüs

Vakaların %85'i Finlandiya ve Almanya'dan

Hantavirus infection. In: ECDC. Annual epidemiological report for 2020

AVRUPA KITASI

Figure 1. Distribution of hantavirus infection rates per 100 000 population by country, EU/EEA, 2020



Source: country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

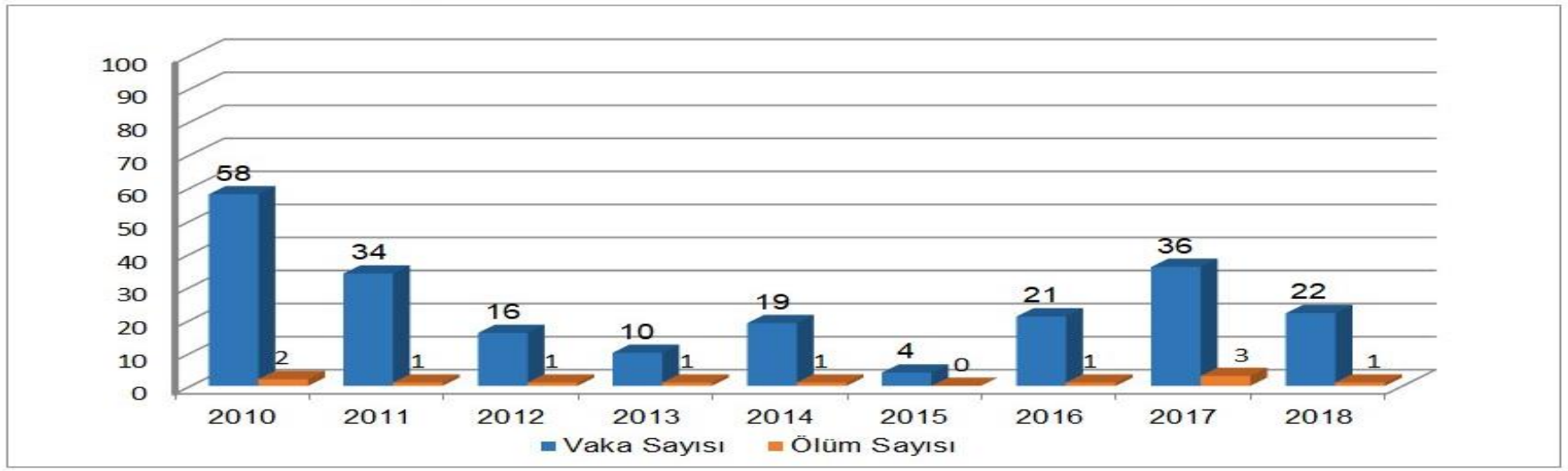
Hantavirus infection. In: ECDC. Annual epidemiological report for 2020

TÜRKİYE

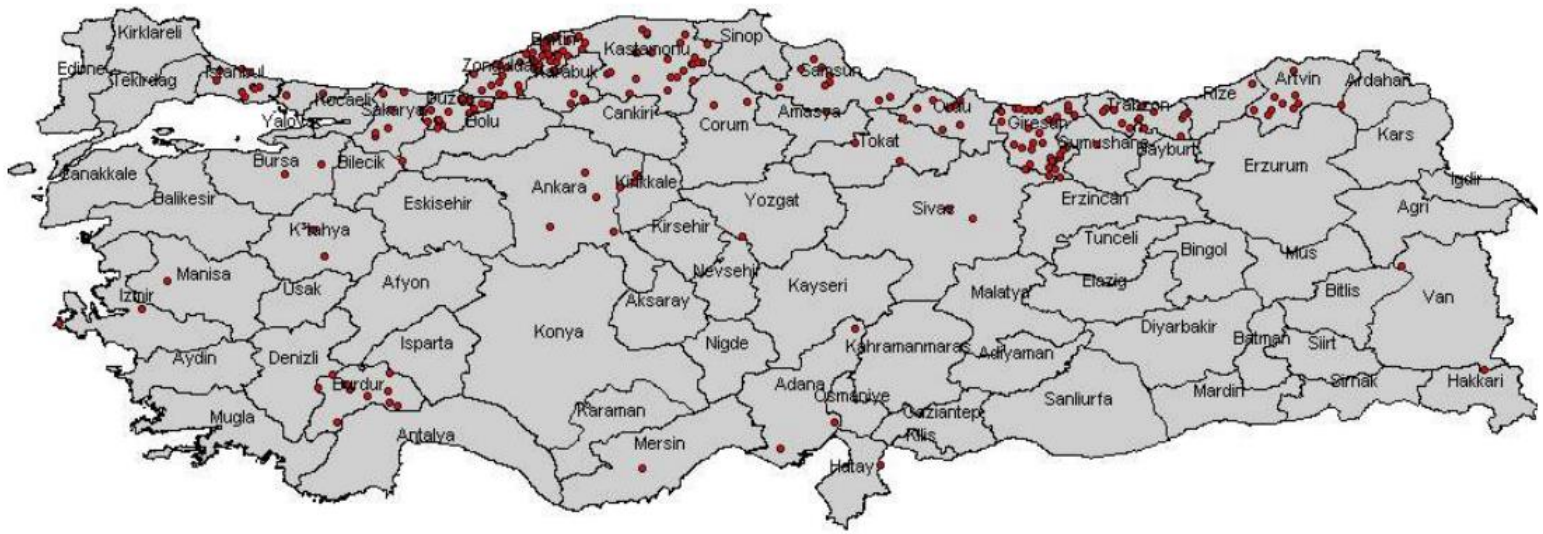
Vaka ve Ölüm Sayıları, Morbidite ve Mortalite Hızları, Türkiye, 2010-2018

Yıllar	Nüfus	Vaka Sayısı	Morbidite Hızı (100.000)	Ölüm Sayısı	Mortalite Hızı (1.000.000)
2010	73.722.988	58	0,08	2	0,03
2011	74.724.269	34	0,05	1	0,01
2012	75.627.384	16	0,02	1	0,01
2013	76.667.864	10	0,01	1	0,01
2014	77.695.904	19	0,02	1	0,01
2015	78.741.053	4	0,01	0	0,00
2016	79.814.871	21	0,03	1	0,01
2017	80.810.525	36	0,04	3	0,04
2018	82.003.882	22	0,03	1	0,01

Grafik 1. Hantavirüs Enfeksiyonu Vakalarının ve Ölümlerinin Yıllara Göre Dağılımı, Türkiye, 2010-2018



İllere Göre Vakaların Dağılımı, Türkiye, 2009-2017



TÜRKİYE

- 2009-2018 arasında; 239 olgu, 13 ölüm vaka-ölüm oranı %5,44

- Ülkemizde, hantavirüs tiplerinden Dobrava (DOBV), Puumala (PUUV), Saaremaa (SAAV), Tula (TULV) ve Seoul (SEOV) virüslerinin taşıyıcısı olan kemirici türleri bulunmaktadır

- Vakaların çoğunda PUUV ve DOBV

GİRESUN

- 2020 sonrası 13 hantavirus vakası
- 11 erkek 2 kadın tamamı **kırsal** kesimden
- **Fare çıktılarıyla** temas anamnezi 5 hasta
- Diyaliz ihtiyacı 5 hasta
- Renal fonksiyonları normale dönen hasta sayısı 9
- Yoğun bakım yatış 3 hasta
- Mortalite 3/13

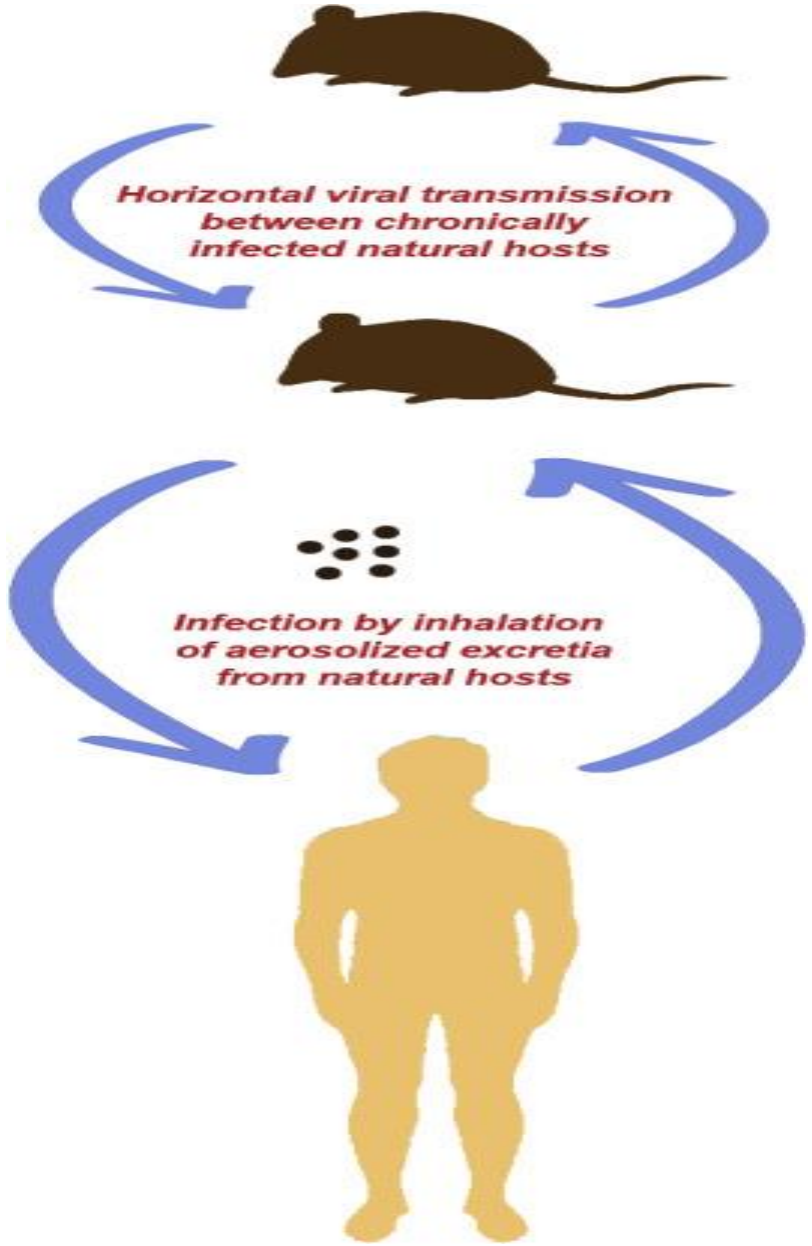
BULAŞ

- Fare çıkartılarıyla direkt temas(idrar, feçes, tükürük)
- Kemiriciler tarafından ısırılma
- Havayolu ile direkt bulaşma
- İnsandan insana bulaş

BULAŞ

Doğada, hantavirüsler, kronik olarak enfekte olmuş doğal konak rezervuarları (fareler, sıçanlar, tarla fareleri) arasında yatay geçiş yoluyla dolaşmaktadır.

Çoğu insan, enfeksiyonu kontamine aerosol haline getirilmiş kemirgen dışkısını soluduğunda alır.



RİSK GRUPLARI

- Uzun süre kullanılmayan binaları, odunluk depo gibi alanları temizleyenler
- Kampçılar
- Askerler
- Orman işçileri, çiftçiler
- Laboratuar çalışanları

PATOGENEZ

- İnhalasyonla alınan virüs doku makrofajları ile bölgesel LN
- LN'nda replike olup primer viremi ile hedef organa ulaşır

- Hedef organın endotelinde replike olur.(ac,kalp, bb, lenfoid organlar)
- Endotel hc girebilmek için β3 integrin reseptörüne tutunurlar. (trombosit ve makrofaj hc membranında da var)

- Hedef hc lerin enfekte olması ile immun sistem aktive olur.(direkt sitopatik etki göstermez)
- IL1, IL6 TNFα…. Vasküler permeabilite artar

- CD8 T lenfositler de enfekte hc yıkımında rol oynar. CD4/CD8 oranı terse döner!

PATOGENEZ

- Klinik tablo endotel ve epitel bariyerinin işlev bozukluğu ile ilişkilidir.

Ancak patogenez tam aydınlatılamamıştır!

KLİNİK

- Kliniği ve hastalığın şiddetini etkileyen faktörler
  - -Hantavirus tipi
  - -Serumdaki Hantavirus RNA seviyesi
  - -Bireysel İmmunite
  - -HLA-B27 aleline sahip olanlarda hafif seyir?
  - -HLA-B8 aleline sahip bireylerde HD ihtiyacı daha fazla?
  - -Yükselmiş anjiopoietin2/1 oranının hastalığın ciddiyeti

KLİNİK

- **Eski dünya virüsleri**
  -Avrupa ve Asya'da bulunur
  -Klinik HFRS(Hemorrhagic Fever with Renal Syndrome) ve Nefropatia epidemika
  -Puumala, Hantaan, Dobrava ve Seoul virüs

- **Yeni dünya virüsleri**
  -Amerika kıtası
  -Klinik HPS(Hantavirus Pulmonary Syndrome)/HCPS
  -Sin Nombre, Andes, Laguna Negra, New York

İnkübasyon periyodu HFRS de 10-42g, HPS de 9-33 gündür.

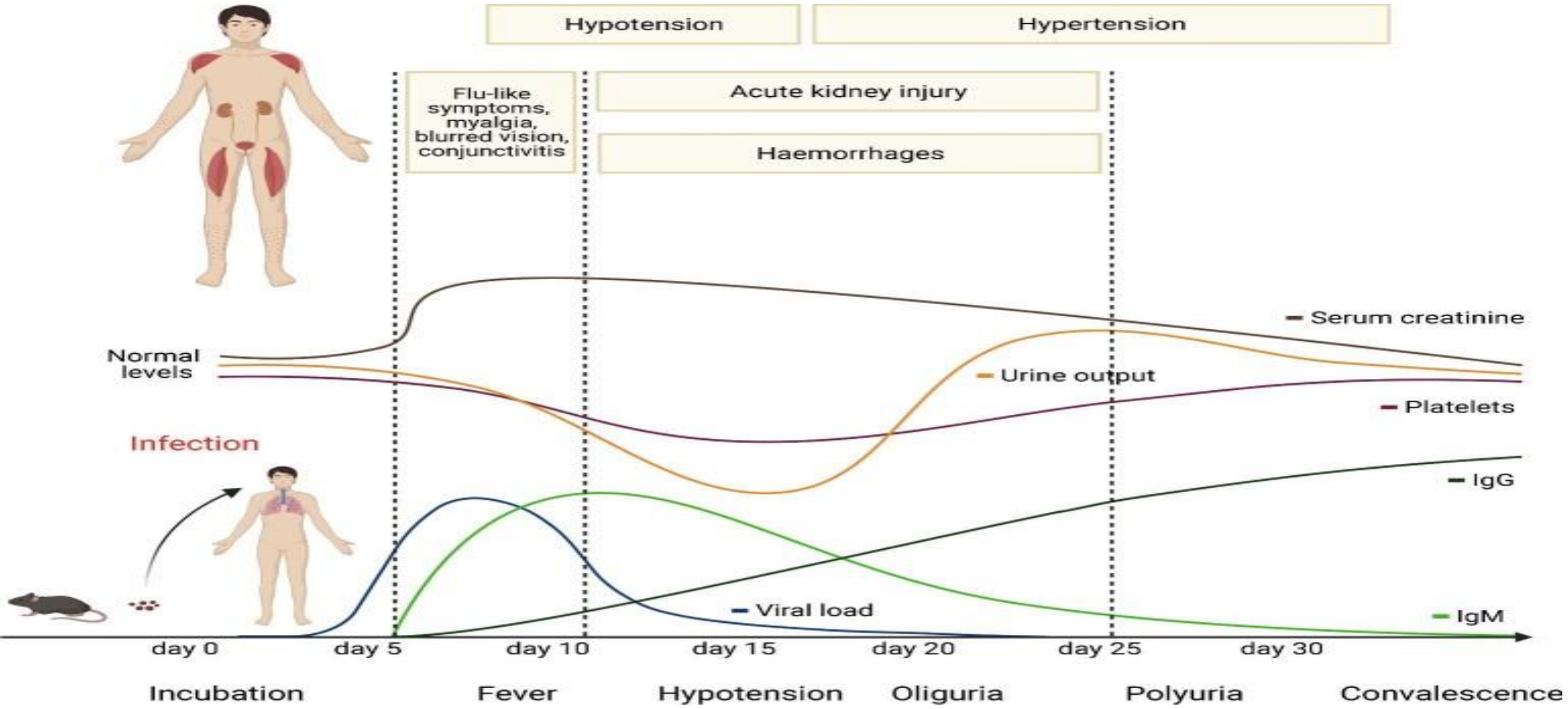
Worldwide prevalence of hantaviruses that cause disease in humans

Virus	Reservoir hosts	Countries where disease has been reported	Distribution of reservoir host	Disease
Hantaan	*Apodemus agrarius*	China, Korea, Russia	Central Europe south to Thrace, Caucasus, and Tien Shan Mountains; Amur River through Korea to eastern Xizang and eastern Yunnan, western Sichuan, Fujiau, and Taiwan	HFRS
Seoul	*Rattus norvegicus, Rattus rattus*	China, Korea, United Kingdom (rare), United States (rare)	Worldwide; commensal rat hosts	HFRS
Dobrava/Belgrade	*Apodemus flavicollis*	Widespread throughout central and western Europe	England and Wales; from northwestern Spain, France, southern Scandinavia through Russia to Urals, southern Italy, the Balkans, Syria, Lebanon, and Israel	HFRS
Puumala	*Myodes glareolus*	Scandinavia, western Europe, Russia	Western Palaearctic from France and Scandinavia to Lake Baikal, south to northern Spain, northern Italy, Balkans, western Turkey, northern Khazakhstan, Altai and Sayan Mountains, Britain, and southwestern Ireland	HFRS
Sin Nombre	*Peromyscus maniculatus*	United States, Canada	Alaska panhandle across northern and western Canada, south through most of the continental United States excluding southeastern and eastern seaboard, to southernmost Baja California Sur, and to north central Oaxaca, Mexico	HCPS
Black Creek Canal	*Sigmodon hispidus*	United States (only reported in Florida)	United States, from southern Nebraska to central Virginia, south to southeastern Arizona and peninsular Florida; interior and eastern Mexico through Middle America to central Panama; in South America to northern Colombia and northern Venezuela	HCPS
New York	*Peromyscus leucopus*	United States (may be restricted to Long Island, New York)	Central and eastern United States to southern Alberta and southern Ontario, Quebec and Nova Scotia, Canada; to northern Durango and along Caribbean coast to isthmus of Tehuantepec and Yucatan peninsula, Mexico	HCPS
Bayou	*Oryzomys palustris*	United States	Southeastern United States, southeastern Kansas to eastern Texas, eastward to southern New Jersey and peninsular Florida	HCPS
Andes	*Oligoryzomys longicaudatus*	Brazil, Chile, Argentina	North central to southern Andes, approximately to 50¼S latitude, of Chile and Argentina	HCPS
Laguna Negra	*Calomys laucha*	Paraguay, Bolivia	Northern Argentina and Uruguay, southeastern Bolivia, western Paraguay, and west central Brazil	HCPS
Choclo	*Oligoryzomys fulvescens*	Panama	Southern Mexico, through Mesoamerica, to Ecuador, northernmost Brazil, and Guineas in South America	HCPS
Rio Mamore	*Oligoryzomys microtis*	Peru	Bolivia, Peru, Brazil, Paraguay, and French Guiana	HCPS

HFRS: hemorrhagic fever with renal syndrome; HCPS: hantavirus cardiopulmonary syndrome.

HFRS

- Avrupa ve Asya'da görülür
- Hastalığın seyrinde beş dönem mevcuttur: febril dönem, hipotansif dönem, oligürik dönem, poliürik dönem ve konvalesan dönem
- Hantaan ve Dobrova enfeksiyonlarında daha şiddetli semptomlar görülürken, Saaremaa, Seoul, Puumala enfeksiyonlarında semptomlar orta derecededir.
- Uzun dönem komplikasyonlar nadirdir (glomerulonefrit, Guillain-Barre sendromu, hipertansiyon, hipopitüitarizm)
- Konjunktivalarda kızarıklık, yüz, boyun ve sırtta kızarıklık, periorbital ödem, relatif bradikardi tipiktir
- Kanama hastaların %10'unda görülür. Mortalite %1 den azdır



Clinical Kidney Journal, 2022, vol. 15no. 7,1231-1252

HCPS

- Amerika Kıtasında
- Hipoksi

- Sin Nombre, Andes, Laguna Negra, New York, Bayou…

- Akciğer grafisinde intertisyel ödem belirgindir, daha sonra bilateral alveoler ödem gelişir

- Mortalite oranı %30–40

- Çocuklarda görülen semptom ve bulgular erişkinlerdekilere benzer ancak klinik oldukça hafif

Journal of Clinical Virology 101 (2018) 66–68

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Short communication

Severe hantavirus disease in children

Tamara K. Dzagurova[a], Evgeniy A. Tkachenko[a,b], Aydar A. Ishmukhametov[a,b], Mariya V. Balovneva[a], Boris Klempa[c,d], Detlev H. Kruger[c,*]

[a] Chumakov Federal Scientific Center for Research and Development of Immune-and Biological Products of Russian Academy of Sciences, Moscow, Russia
[b] 1th Moscow State Medical University "I. M. Sechenov", Moscow, Russia
[c] Institute of Medical Virology, Helmut-Ruska-Haus, Charité School of Medicine, Berlin, Germany
[d] Biomedical Research Center, Institute of Virology, Slovak Academy of Sciences, Bratislava, Slovakia

ARTICLE INFO

Keywords:
Hantavirus disease
Sochi virus
Hemorrhagic fever with renal syndrome
Case fatality rates

ABSTRACT

Background: Very recently, a novel European hantavirus, Sochi virus, has been discovered which causes severe courses of hantavirus disease with a case fatality rate of about 15 percent.
Objectives: We aimed to study to which extent and with which clinical severity children were affected by Sochi virus infection.

Sochi virüs(2012)
Renal+pulmoner tutulum
6 çocuk, 56 yetişkin hasta
(3ü ***ağır*** ,3ü **orta** şiddetli klinik)
Her 2 grupta da benzer prognoz

Table 1. General features of HFRS, NE and HCPS

	HFRS	NE	HCPS
Common features	sudden fever, prostration, myalgia and abdominal discomfort		
Symptoms	hemorrhage, petechiae, inflammatory symptoms of the eye, acute myopia, varying degrees of acute renal failure		dry cough, rapidly increasing dyspnea On chest radiography, rapidly evolving bilateral interstitial edema
Clinical phases	five phases (febrile, hypotensive, oliguric, polyuric, convalescent)	five phases (febrile, hypotensive, oliguric, polyuric, convalescent)	three phases (prodromal, cardiopulmonary, convalescent)
Main target organ	kidneys	kidneys	lungs
Morbidity rate	1%–12%	0.1%–1.0%	40%–50%
Complications	acute encephalomyelitis, bleeding, multiorgan dysfunction, pituitary hemorrhage, glomerulonephritis, pulmonary edema, shock, acute respiratory distress syndrome, disseminated intravascular coagulation, lethal outcome	acute encephalomyelitis, bleeding, multiorgan dysfunction, need of dialysis, perimyocarditis, pituitary hemorrhage, pulmonary edema, shock, lethal outcome	renal insufficiency, thrombocytopenia, bleeding, myalgia, headache, nausea, vomiting, diarrhea, shock, lethal outcome

Note: HFRS, hemorrhagic fever with renal syndrome; NE, nephropathia epidemica; HCPS, hantavirus cardiopulmonary syndrome. NE is a mild form of HFRS. (Maes et al., 2009; Papa, 2012; Mustonen et al., 2013; Jiang et al., 2016)

Jiang H, Zheng X, Wang L, Du H, Wang P, Bai X. Hantavirus infection: a global zoonotic challenge. Virol Sin. 2017 Feb;32(1):32-43. doi: 10.1007/s12250-016-3899-x. Epub 2017 Jan 23. PMID: 28120221; PMCID: PMC6598904.

Open Forum Infectious Diseases

BRIEF REPORT

Acute Hantavirus Infection Presenting With Fever and Altered Mentation in the Absence of Pulmonary or Renal Manifestations

Stephen J. Fawcett,[1] Jeffrey S. Chen,[2] and Richard W. Fawcett[2]

[1]Washington State University, Pullman, Washington, USA, and [2]Columbia Sands Medical Specialties, LLC, Redmond, Oregon, USA

Illness caused by hantaviruses is often severe and is typically characterized by diffuse pulmonary disease or renal insufficiency depending on the type of hantavirus. Here we report 2 cases of hantavirus infection that resulted in severe cognitive impairment but did not have any pulmonary or renal manifestations. These 2 cases may be indicative of previously underreported symptoms of hantavirus infection and might represent examples of hantavirus-related encephalopathy.

Keywords. hantavirus pulmonary syndrome; orthohantavirus.

Introduction

Orthohantaviruses
that are spread zoo
cally cause hemorri
hantavirus pulmo
World" hantavirus
common in Asia ar
viruses are found i
HFRS (caused by
Puumala viruses) can have a mortality rate of up to 15% [3], whereas HPS, caused by Sin Nombre virus (SNV) and Andes virus, has a mortality rate of up to 40% [4]. SNV is typically found in North America and is transmitted through exposure to the urine, feces, or saliva of *Peromyscus maniculatus* (deer mouse) [5]. Other rodents are responsible for transmission of other hantaviruses, and rare human-to-human transmission has only been reported with Andes virus. Hantaviruses generally have an incubation period of 1–5 weeks and infect endothelial cells, altering vascular permeability. Treatment consists of supportive care, and severe cases may require the use of mechanical ventilation or extracorporeal membrane oxygenation.

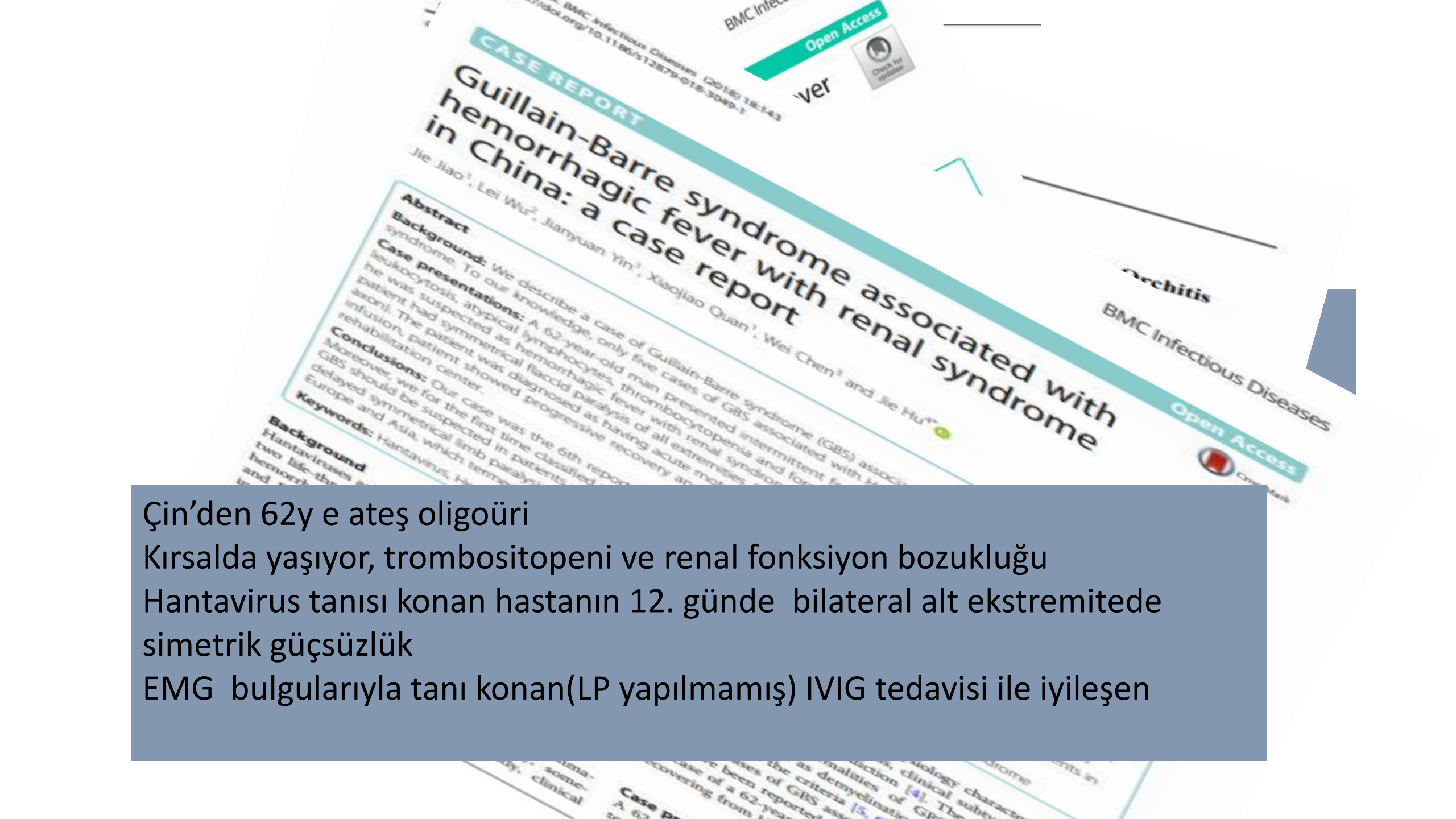
Case 1

In July 2020, a 70-year-old White man was admitted to a hospital in Oregon for confusion, headache, and fever. The patient's wife recalled that they had recently encountered rodents and rodent excrement around their property. His admission laboratory tests were notable for thrombocytopenia of 57,000 platelets/μL; the remainder of the tests were unremarkable. His admission imaging studies included a noncontrast brain computed tomography (CT) and a noncontrast chest CT, both of which showed no acute abnormalities (Figure 1). A lumbar puncture was performed on hospital day 1 and revealed the following cerebrospinal fluid (CSF) results: white blood cell (WBC) count, 1 cell/nL; red blood cell count, 134 cells/nL; protein, 94 mg/dL; and glucose, 93 mg/dL. Three days after admission, brain magnetic resonance imaging
mild sub-
obiologic
nd blood
s positive
(IgG) an-
tive care;
elet count
14 in im-
erformed
pathogen
as SNV using a SNV-specific enzyme-linked immunosorbent assay (ELISA).

Case 2

In February 2021, a 66-year-old White man with type 2 diabetes mellitus, hypertension, and chronic lower back pain was transferred from an outside facility to a regional hospital in Oregon for acute onset of severe confusion, agitation, headache,

Ateş trombositopeni bilinç bulanıklığı, ev çevresinde fare dışkısı anamnezi
Pulmoner ve renal tutulum yok
Sın Nobre



Çin’den 62y e ateş oligoüri

Kırsalda yaşıyor, trombositopeni ve renal fonksiyon bozukluğu

Hantavirus tanısı konan hastanın 12. günde bilateral alt ekstremitede simetrik güçsüzlük

EMG bulgularıyla tanı konan(LP yapılmamış) IVIG tedavisi ile iyileşen

TANI

- Laboratuvar bulguları: lökositoz, trombositopeni, serum kreatininde artış, hematüri, proteinüri

- Serolojik testler (IgM, IgG):ELISA, IFA, Immunoblot

  Serumda IgM pozitifliği ve/veya IgG' de dört kat artış (ELİSA, IFA, İmmünoblot) saptanması

- Hasta başı ımmunokromotografik IgM
- Moleküler testler: RT PCR erken dönemde
- Hücre kültürü: genellikle kemiriciden izole edilir
- Tip tayini: viral nötralizasyon testi

HSGM Güncel Çalışılan Analiz Listesi

					serotiplendirme	Uygun taşıma besiyerinde izolat		
261	Solunum Yolu Patojenleri L.		908.339	Haemophilus influenzae serotiplendirme (Moleküler yöntemle)	Real Time PCR	1 mL BOS, 1 mL Steril vücut sıvısı, Uygun taşıma besiyerinde izolat	3	***
262	Aşı ile Önlenebilir Bakteriyel Hastalıklar Seroloji L.		140.602	*Haemophilus influenzae* tip b IgG (Hib)	ELISA	1 mL Serum	3	278
263	Solunum Yolu Patojenleri L.	30.285	905.990	*Haemophilus* kültürü	Kültür	Nazofarinks sürüntüsü, 1 mL BOS, 1 mL Steril vücut sıvısı	5	***
264	Viroloji L.		120.194	Hantavirus Antikoru, IgG	ELISA	2 mL Serum	5	410
265	Viroloji L.	40.079	120.190	Hantavirus Antikoru, IgG	IFA	2 mL Serum	5	410
266	Viroloji L.	40.098	120.198	Hantavirus Antikoru, IgG	Immunblotting	2 mL Serum	5	420
267	Viroloji L.		190.207	Hantavirus Antikoru, IgG	Line Immunoassay (LIA)	2 mL Serum	5	540
268	Viroloji L.		120.196	Hantavirus Antikoru, IgM	ELISA	2 mL Serum	5	410
269	Viroloji L.	40.080	120.192	Hantavirus Antikoru, IgM	IFA	2 mL Serum	5	410
270	Viroloji L.	40.029	120.197	Hantavirus Antikoru, IgM	Immunblotting	2 mL Serum	5	420
271	Viroloji L.		190.208	Hantavirus Antikoru, IgM	Line Immunoassay (LIA)	2 mL Serum	5	540
272	Viroloji L.		120.199	Hantavirus Dobrova PCR	Real Time PCR	2 mL EDTA'lı tüpte tam kan veya EDTA'lı plazma, 2 mL Serum	3	895
273	Viroloji L.		120.200	Hantavirus Puumala PCR	Real Time PCR	2 mL EDTA'lı tüpte tam kan veya EDTA'lı plazma, 2 mL Serum	3	895
274	Paraziter Hast. L.	30.204	912.320	Helmint (Kato-katz; helmint yumurtaları)	Mikroskobi	5 g Dışkı	3	***
275	HIV-AIDS ve Viral Hepatitler L.		906.520	Hepatit A IgG antikoru (Anti HAV IgG)	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	3	***
276	HIV-AIDS ve Viral Hepatitler L.		906.540	Hepatit A IgM antikoru (Anti HAV IgM)	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	3	***
277	HIV-AIDS ve Viral Hepatitler L.		120.184	Hepatit B s antijeni (HBsAg) Doğrulama	ELISA / ELFA	2 - 4 mL EDTA'lı tüpte tam kan/ plazma/serum	5	450
278	HIV-AIDS ve Viral Hepatitler L.		907.450	Hepatit B yüzey Antijeni (HBsAg)	ELISA / ELFA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	3	***
279	HIV-AIDS ve Viral Hepatitler L.		906.570	Anti -Hbc Ig M	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	5	***
280	HIV-AIDS ve Viral Hepatitler L.		906.550	Anti Hbc Ig G	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	5	***
281	HIV-AIDS ve Viral Hepatitler L.		906.590	Anti Hbe	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	5	***
282	HIV-AIDS ve Viral Hepatitler L.		907.410	HbeAg	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	5	***
283	HIV-AIDS ve Viral Hepatitler L.		906.610	Anti-Hbs	ELISA	2 mL EDTA'lı tüpte tam kan/ plazma/serum	5	***
284	HIV-AIDS ve Viral Hepatitler L.	40.074	908.150	Hepatit B Virüs (HBV) DNA PCR, Kantitatif	Real Time PCR	4 mL EDTA'lı tüpte tam kan/ EDTA'lı plazma/Serum/**Klinik dışı örnek**	5	***
285	HIV-AIDS ve Viral Hepatitler L.		120.218	Hepatit B Virüs (HBV) Genotiplendirme ve Antiviral İlaç Direnç Analizi	PCR ve sekans analizi	4 mL EDTA'lı tüpte tam kan/ EDTA'lı plazma	10	3400

AYIRICI TANI

- Viral hemorajik ateş patogenezi benzer(Sarı Humma,Dengue, Lassa, KKKA,Ebola…)
- Leptospiroz
- Sepsis
- Meningokoksemi
- Riketsiyal hastalıklar
- Pyelonefrit
- İnfuenza
- COVID-19

AYIRICI TANI

- Mayıs 2009 ile Ocak 2012 tarihleri arasında hantavirüs enfeksiyonu ön tanısı ile hastaneye başvuran 100 hasta

  Grup1: 20 hanta pozitif

  Grup2: 35 leptospiroz,15 KKKA, 10 tifo, 5 Gram negatif bakteriyemi, 15 noninf.

G1:

Proteinüri, hematüri, kas ağrısı ve ishal/karın ağrısı Grup 1'de Grup 2'ye göre anlamlı olarak yüksekti ($P < 0.05$).

Serum üre, cre, ürik asit, LDH, AST, ALP ve CRP anlamlı olarak yüksekti, ancak serum trombosit sayıları daha düşüktü. ($P < 0.05$).

CRP'nin 2,5 mg/dl'nin altında olması %100 negatif bir prediktif faktör olarak kullanılabileceğini ortaya koymuştur.

Hanta/Lepto alt grup analizinde ; Hantavirüs hastalarında hasta yaşı, serum üre, kreatinin, LDH ve AST düzeyleri, leptospiroz olgularında ise WBC daha yüksekti. Hantavirüs enfeksiyonlu hastalarda serum trombosit seviyeleri daha düşüktü.

- Bu çalışmada hastanede ölen hastaların serum PCT, CPK ve miyoglobin düzeylerinin sağlıklı taburcu edilen hastalara göre anlamlı olarak yüksek olması dikkat çekicidir.(2hasta)

Can Hantavirus Infections Be Predicted on Admission to Hospital?

Selçuk Kaya,[1]* Dilek Yağcı Çağlayık,[2] Yavuz Uyar,[2] Hava Yılmaz,[3] Aynur Engin,[4] Pınar Öngürü,[5] Gurdal Yılmaz,[1] and Iftihar Köksal[1]
[1]Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Karadeniz Technical University, Trabzon, Turkey
[2]Refik Saydam National Public Health Agency (RSNPHA), Ankara, Turkey
[3]Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Cumhuriyet University, Sivas, Turkey
[5]Department of Infectious Diseases and Clinical Microbiology, Numune Education and Research Hospital, Ankara, Turkey

The aim of this study was to investigate the predictive factors which contribute to diagnosis of hantavirus infection. One hundred patients from rural areas hospitalized with a preliminary diagnosis of hantavirus infection from different hospitals in Turkey were investigated. Hantavirus infection was confirmed in 20 patients (Group 1) using immunofluorescence and immunoblot assays at the Refik Saydam National Public Health Agency. Hantaviruses were not detected in the serum of the remaining 80 patients, other infectious and non-infectious diseases being diagnosed in this group (Group 2). Patients' demographic characteristics and clinical and laboratory data on admission were examined and compared between the two groups. Fever, proteinuria, hematuria, lethargy-weakness, and nausea-vomiting were the most frequent symptoms and findings in Group 1, seen in almost all patients. Proteinuria, hematuria, muscle pain, diarrhea/abdominal pain, hypotension, shock, and sweating were observed at significantly higher levels in Group 1 compared to Group 2. Serum urea, creatinine, uric acid, lactate dehydrogenase (LDH), aspartate transaminase (AST), alkaline phosphatase (ALP), and C-reactive protein (CRP) were significantly higher, but serum platelet counts were lower in Group 1 patients. Area beneath the receiver operating characteristics (ROC) curve analysis was used to calculate the discriminative ability of various laboratory values to identify patients with hantavirus infection. This analysis revealed that, serum CRP had a 100% negative predictive value, whilst, platelet, and creatinine had 75% and 70% positive predictive values for the diagnosis of hantavirus infection. In summary, laboratory markers used in clinical practice are of great importance predicting hantavirus infections. *J. Med. Virol. 84:1790–1796, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: hantavirus failure with renal syndrome; predictive factors; diagnosis

INTRODUCTION

Hemorrhagic fever renal syndrome (HFRS) is found almost worldwide and represents an important public health problem, with 20,000–50,000 human cases being diagnosed annually [Wu et al., 2011]. While subtypes such as Saaremaa, Puumala, seen in Central Europe and Scandinavian countries lead to mild infections, Hantaan (HTNV), Dobrava (DOBV), and Seoul (SEOV), seen in Asia and Europe, cause moderate-severe infections [Laakkonen et al., 2006; Kariwa et al., 2007; Vaheri et al., 2008; Heyman et al., 2009, 2011]. Mortality may be as high as 15% in severe forms [Klein et al., 2011]. Since the DOBV subtype is seen in Turkey, neighboring Balkan countries and Russia, it is of particular importance to Turkey [Klempa et al., 2008; Ertek and Buzgan, 2009; Kaya et al., 2010; Maftei et al., 2011; Oncul et al., 2011].

All authors declared that they have no conflict of interest.
*Correspondence to: Selçuk Kaya, Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Karadeniz Technical University, Trabzon 61080, Turkey.
E-mail: eselkaya@yahoo.com
Accepted 25 June 2012
DOI 10.1002/jmv.23390
Published online in Wiley Online Library (wileyonlinelibrary.com).

AYIRICI TANI

- Ocak 2000-2019 arası 162 hasta
- L:92 H:70
- İstatistiksel olarak anlamlı farklılık gösterdiği belirlenen beş parametre
- Leptospiroz ayrımında MICE skoru ≥ 3, %93,5 duyarlılık, %92,9 özgüllük, PPV %94,5 ve NPV %91,5.

ORIGINAL PAPER

The "MICE" scoring system in differentiating the identical twins leptospirosis and hantavirus infection

Selçuk Kaya[1] · Gürdal Yılmaz[1] · Murat Aydın[1] · Firdevs Aksoy[1] · İftihar Koksal[1]

Received: 29 May 2019 / Accepted: 15 October 2019 / Published online: 26 October 2019

Abstract

Purpose To develop a practical scoring system to assist clinicians in differentiating leptospirosis and hantavirus infections, whose epidemiological, clinical, and laboratory characteristics are literally like identical twins.

Methods The study population consisted of 162 patients admitted to hospital with a confirmed diagnosis of leptospirosis (LG group, $n = 92$) and hantavirus infections (HG, group = 70) between January 2000 and January 2019. The two groups were compared in terms of demographic, clinical and laboratory features. Sensitivity, specificity, and positive and negative predictive values were determined from ROC analysis for findings of significance in the diagnosis of leptospirosis, and a scoring system for diagnosis was developed ("MICE" score). During the development of this scoring system, we were careful to employ parameters that would not affect one another statistically, to reflect the involvement of very different systems (such as the hematological, hepatic, renal, and musculoskeletal systems) due to the multisystemic effect of the disease in the organism, and to ensure that the system should be simple to apply and understand. Accordingly, five parameters, serum WBC, creatinine, creatine kinase, total bilirubin, and C-reactive protein, were employed in the "MICE" scoring system.

Results Three cut-off values were determined using ROC analysis for the five parameters included in the MICE system.

Table 1 Calculation table representing the basis of the "MICE" scoring system

From: The "MICE" scoring system in differentiating the identical twins leptospirosis and hantavirus infection

Parameter	Value	Score
WBC (/μL)	≤ 7500	0
	7500–15,000	1
	> 15,000	2
Total bilirubin (mg/dL)	≤ 3	0
	3–10	1
	> 10	2
CRP (mg/dL)	≤ 5	0
	5–15	1
	> 15	2
Creatinine (mg/dL)	≤ 1.5	0
	1.5–3	1
	> 3	2
CK (U/L)	≤ 500	0
	500–1000	1
	> 1000	2

WBC white blood cell, *CRP* C-reactive protein, *CK* creatine kinase

- IL6
- Pentraxin3(PTX3)
- Indoleamin2,3 Dioksijenaz(IDO)
- Resistin

Hastalığın şiddeti ile korele

- PCT
- CRP

Artmış PCT ve CRP ciddi hastalıkla ilişkilendirilmesinde çelişkili sonuçlar

viruses

MDPI

Review

Severity Biomarkers in Puumala Hantavirus Infection

Tuula K. Outinen [1,2,*], Satu Mäkelä [1,2], Ilkka Pörsti [1,2], Antti Vaheri [3] and Jukka Mustonen [1,2]

[1] Department of Internal Medicine, Tampere University Hospital, Elämänaukio 2, 33520 Tampere, Finland; satu.m.makela@pshp.fi (S.M.); ilkka.porsti@tuni.fi (I.P.); jukka.mustonen@tuni.fi (J.M.)
[2] Faculty of Medicine and Health Technology, Arvo Ylpön katu 34, Tampere University, 33014 Tampere, Finland
[3] Department of Virology, Medicum, University of Helsinki, 00290 Helsinki, Finland; antti.vaheri@helsinki.fi
* Correspondence: tuula.outinen@gmail.com

Abstract: Annually, over 10,000 cases of hemorrhagic fever with renal syndrome (HFRS) are diagnosed in Europe. Puumala hantavirus (PUUV) causes most of the European HFRS cases. PUUV causes usually a relatively mild disease, which is rarely fatal. However, the severity of the infection varies greatly, and factors affecting the severity are mostly unrevealed. Host genes are known to have an effect. The typical clinical features in PUUV infection include acute kidney injury, thrombocytopenia, and increased vascular permeability. The primary target of hantavirus is the endothelium of the vessels of different organs. Although PUUV does not cause direct cytopathology of the endothelial cells, remarkable changes in both the barrier function of the endothelium and the function of the infected endothelial cells occur. Host immune or inflammatory mechanisms are probably important in the development of the capillary leakage. Several immunoinflammatory biomarkers have been studied in the context of assessing the severity of HFRS caused by PUUV. Most of them are not used in clinical practice, but the increasing knowledge about the biomarkers has elucidated the pathogenesis of PUUV infection.

Keywords: hantavirus; hemorrhagic fever with renal syndrome; Puumala virus; biomarker

Citation: Outinen, T.K.; Mäkelä, S.; Pörsti, I.; Vaheri, A.; Mustonen, J. Severity Biomarkers in Puumala Hantavirus Infection. *Viruses* **2022**, *14*,

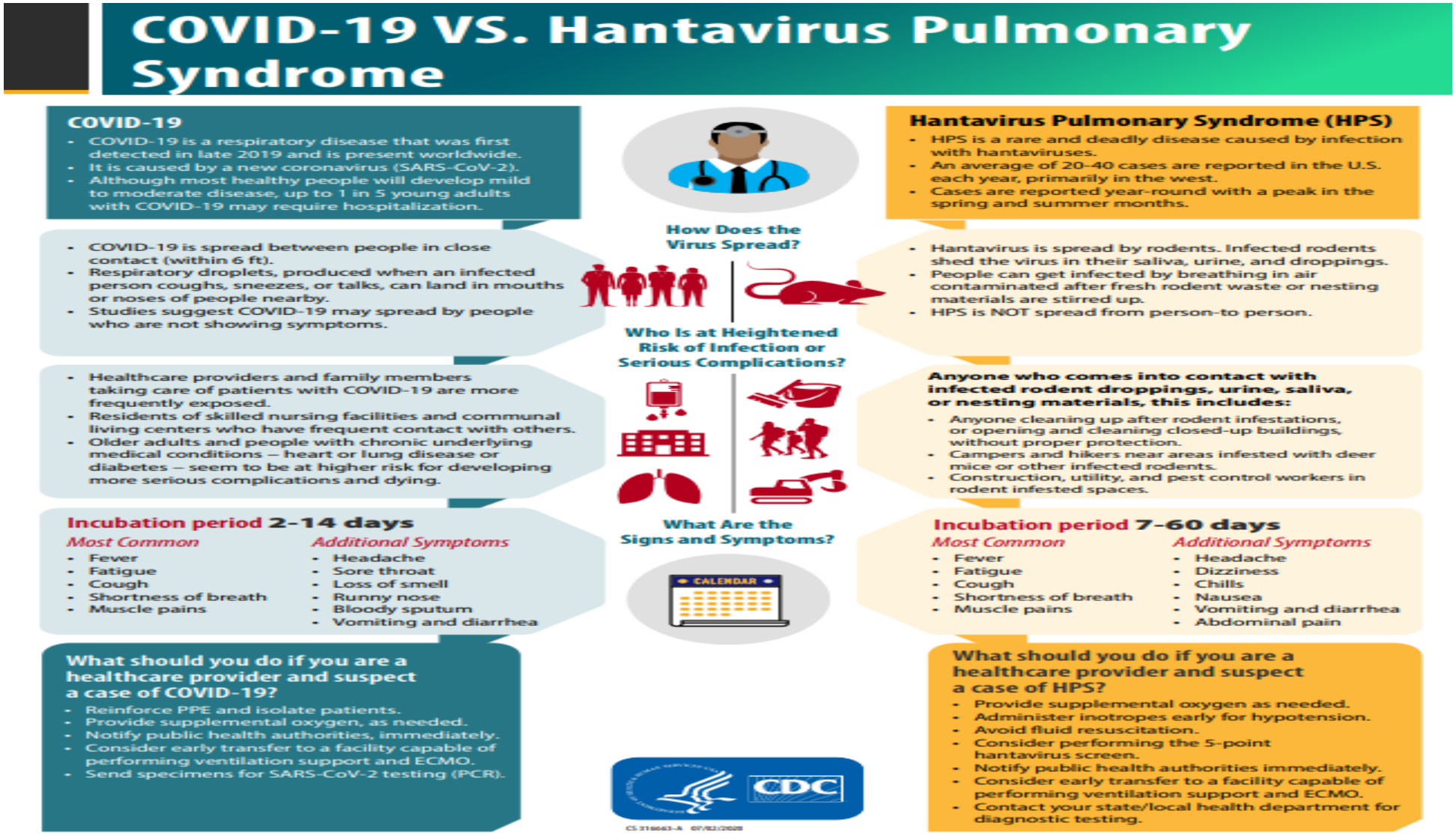
Published: 28 December 2021

1. Introduction

Hantaviruses are enveloped viruses with a trisegmented viral RNA genome [1]. The …nedium, and large encode the nucleocapsid protein N, the two …c, and the RNA polymerase, respectively [1]. Hantaviruses can …romes in humans, i.e., hemorrhagic fever with renal syndrome …sia, and hantavirus cardiopulmonary syndrome (HCPS) in the …aan virus (HTNV), Puumala virus (PUUV) and Dobrava–Belgrade …RS in Eurasia. The Seoul virus (SEOV) causing HFRS is a global pathogen [1–3]. Over 10,000 HFRS cases are diagnosed annually in Europe [2]. PUUV, carried by the bank vole (*Myodes glareolus*), causes most of the European HFRS cases [4]. The majority of these infections are reported in Finland, which has the highest incidence globally of a diagnosed hantavirus disease, with 1000–3000 serological diagnoses each year [4,5].

PUUV infection is typically associated with increased vascular permeability, acute kidney injury (AKI), and thrombocytopenia [6–10]. Whereas the case fatality rates for HFRS

AYIRICI TANI



Pandemi servisinde yakalanan hantavirus olgusu

Klimik Dergisi 2021; 34(2): 141-3

OLGU SUNUMU CASE REPORT

COVID-19 Pandemisi Sırasında Saptanan Bir Hantavirüs İnfeksiyonu Olgusu

A Case of Hantavirus Infection Detected During the COVID-19 Pandemic

Sinan Çetin[1], Ahmet Melih Şahin[2]

[1]*Dr. Ali Menekşe Göğüs Hastalıkları Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, Giresun, Türkiye;* [2]*Giresun Üniversitesi, Prof. Dr. A. İlhan Özdemir Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, Giresun, Türkiye*

ÖZET

Hantaviruslar, Bunyaviridae ailesinde yer alan ve insanlarda kanamalı ateş ile seyreden renal sendrom (KARS) ve hantavirus kardiyopulmoner sendrom (HKPS) olmak üzere iki ayrı hastalığa yol açan viruslardır. Ülkemizde görülen KARS formu, ateş yüksekliği, akut böbrek hasarı, trombositopeni ve kanamalar ile seyretmektedir. Bu semptom ve bulgular ile başvuran hastalarda ayırıcı tanıda hantavirus infeksiyonları akılda tutulmalıdır. Bu bildiride, "Coronavirus disease 2019" (COVID-19) pandemisi sırasında, COVID-19 ayırıcı tanısıyla takip edilen ve hantavirusa bağlı KARS tanısı alan bir olgu sunulmuştur.

Anahtar Sözcükler: Hantavirus, COVID-19, akut böbrek hasarı, trombositopeni

ABSTRACT

Hantaviruses are viruses belonging to the Bunyaviridae family, and they cause two forms of acute illness in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). HFRS form seen in our country progresses with fever, acute kidney injury, thrombocytopenia and bleeding. Therefore, hantavirus infections should be kept in mind in the differential diagnosis of patients presenting with these symptoms and signs. This report presents a case followed up with the differential diagnosis of coronavirus disease-19 (COVID-19) during the pandemic and diagnosed with HFRS due to hantavirus.

Keywords: Hantavirus, COVID-19, acute kidney injury, thrombocytopenia

GİRİŞ

Hantaviruslar, Bunyaviridae ailesinde yer alan, kemirici (rodent) veya böcekçil (insektivor) kaynaklı bulaş gösteren, zarflı RNA viruslarıdır (1). Bulaş genellikle rodentlerin tükürük, idrar ve gaita gibi çıkartılarının inhalasyonu veya temas yoluyla olmaktadır. İnsanlarda, kanamalı ateşle seyreden renal sendrom (KARS) ve hantavirus kardiyopulmoner sendrom (HKPS) olmak üzere iki farklı tip hastalık oluşturmaktadır (2). KARS, böbrek yetmezliği, kanama, şok ve ateş ile seyretmekte olup daha çok Asya ve Avrupa kıtasında yaygın olarak görülmektedir. HKPS ise akut solunum yet-

TEDAVİ

- Destekleyici tedavi
- Diyaliz
- Trombosit ve diğer kan ürünü replasmanı
- ECMO
- Ribavirin!

Aşı?(Çin ve Kore)

T.C.
SAĞLIK BAKANLIĞI
REFİK SAYDAM HIFZISSIHHA MERKEZİ BAŞKANLIĞI

TÜRK HİJYEN ve DENEYSEL BİYOLOJİ DERGİSİ

Cilt/Vol 68
Sayi/ Number 2
Yil/Year 2011
Ek/Suppl 1

EK / SUPPLEMENT

HANTAVİRÜS SEMPOZYUMU

TURKISH BULLETIN OF HYGIENE AND EXPERIMENTAL BIOLOGY

T.C. SAĞLIK BAKANLIĞI
HALK SAĞLIĞI
GENEL MÜDÜRLÜĞÜ

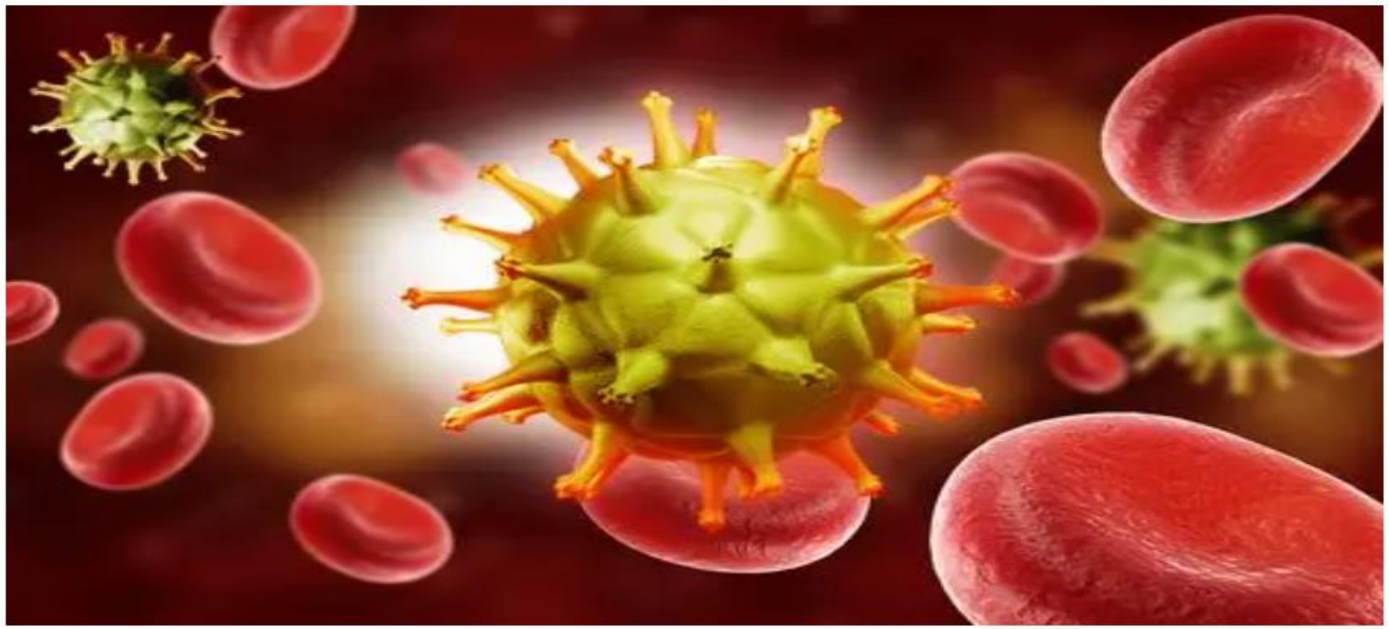
HANTAVİRÜS ENFEKSİYONU*

ANKARA-2020

Türk bilim insanları 4 ölümcül virüs buldu

Türk bilim insanları, kanamalı ateşe neden olan ve böbrek yetmezliğiyle ölüme yol açan 4 virüs tespit etti.

05.08.2019 09:42



Dokuz Eylül Üniversitesi Tıp Fakültesi Tıbbi Viroloji Bilim Dalı Öğretim Üyesi Prof. Dr. Mehmet Ali Öktem yürütücülüğünde Bülent Ecevit Üniversitesi Biyoloji Bölümü Öğretim Üyesi Prof. Dr. Mustafa Sözen ve ekiplerinin katılımıyla **"Türkiye kemirici ve küçük memelilerinde Hantavirüs varlığının ve dağılımının araştırılması"** konulu çalışma başlatıldı.

Araştırma kapsamında kemiricilerden insanlara bulaşan, ateş ve kanama ile seyreden, böbrek yetmezliği nedeniyle ölümcül olabilen **"Dobrava Hantavirus İğneada", "Dobrava Hantavirus Giresun", "Puumala Hantavirus Bartın", "Tuula Hantavirus Palandöken"** adı verilen ve insanlarda çok nadir rastlanan 4 virüs tespit edilerek bilim dünyasına duyuruldu.

SONUÇ

- Hantavirus enfeksiyonu nadir görülen bulaşıcı hastalıklardır
- Avrupada kademeli olarak artmakta

- Dünyanın farklı yerlerinde henüz bilinmeyen patojenik etkiye sahip yeni hantavirusler keşfedilmekte
- İnsandan insana bulaşa neden olabilen yeni türler, salgınlar

- İklim değişikliklerinin olası etkileri

Tüm bunlar enfeksiyon hastalıkları, nefroloji ve halk sağlığının özel çabası ve takibini gerektirmektedir.

SONUÇ

- **Ayrıntılı anamnez**
- **Yerel epidemiyolojiyi bilmek**
- **Klinik bulgular ve lab parametreleri**
- **6 haftayı bulabilen uzun inkubasyon**
- **Atipik klinikle seyreden vakaların olabileceği akılda tutmak**