



Will Hantaviruses Pose Yet Another Health Threat?

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Abstract

Amidst the on-going COVID19 pandemic, the report of the death of a man who tested positive for hantavirus in China came as a tweet from 'Global Times' in late March 2020. This raised fears throughout the world as another possible disease outbreak. With the large number of hantavirus serotypes reported from various parts of the world, the possibility of a health care threat in the form of a zoonotic disease has to be reviewed. The biology of Hantaviruses and the mechanisms of emergence and host-switching in Hantaviruses are briefly reviewed here.

Keywords: Hantavirus; Infectious Diseases; Geographic Distribution; Host-Switching; Zoonotic Viruses; Surveillance

Abbreviations: HFRS: Hemorrhagic Fever With Renal Syndrome; HCPS: Hantavirus Cardiopulmonary Syndrome; HPS: Hantavirus Pulmonary Syndrome; HTNV: Hantaviruses Like Hantaan Virus; PUUV: Puumala Virus; SEOV: Seoul Virus; DOBV: Dobrava Virus.

Introduction

The COVID19 pandemic, emerged as a pneumonia associated with the 2019 novel coronavirus (2019-nCoV) in the city of Wuhan, China, has shaken the entire world putting every human being into the risk [1]. In a couple of months after the start of this pandemic, the report of the death of a man who tested positive for hantavirus came as a tweet from 'Global Times', an English-language publication based in China in late March 2020 [2]. This raised fears throughout the world as another possible disease outbreak. Though official reports and further details on the case are not available yet, the issue triggered the medical fraternity and the scientific community to ponder into the issue.

Hantaviruses are enveloped, negative-sense, single-stranded RNA viruses that belong to the genus Hantavirus and the family Bunyviridae. They have a tripartite genome with three segments small (S), medium (M), and large (L). The main natural reservoir of hantaviruses are rodents which transmit the infection occasionally to human beings who come in contact with the urine and excreta of infected rodents. Rodents can also transmit the virus through direct inoculation by biting. In human beings hantaviruses cause two types of serious illnesses, hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS). In fact, HFRS was first clinically recognized in 1931 in northeast China [3]. HPS was first recognized in 1993 during an outbreak of severe respiratory disease in the Four Corners region of the US [4].

Hantaviruses like Hantaan virus (HTNV), Puumala virus (PUUV), Seoul virus (SEOV) and Dobrava virus (DOBV) are predominantly found in Europe and Asia and are called Old World hantaviruses. They cause HFRS with a case fatality

rate ranging from <1 to 15% that depends upon the type of infecting virus [5]. Other hantaviruses like Andes virus (ANDV), Choclo virus (CHOV) and Sin Nombre virus (SNV) are found predominantly in America and are called New World hantaviruses. They cause HPS with a case fatality rate of up to 40% [6].

Till date Andes virus (ANDV) is the only hantavirus that has been proven to be transmitted from person-to-person as early as 1996 in an outbreak in southern Argentina [7]. This finding of person-to-person transmission of ANDV was confirmed by several other studies through genetic analysis performed on partial sequences of ANDV [8,9]. A latter study by Alonso and team that used full-length virus sequencing provided molecular evidence for the person-to-person transmission of ANDV in a cluster of cases in Argentina [10].

The clinical severity of hantavirus infection in humans varies depending upon the type of infecting virus. In European countries Puumala virus is the most common type that usually causes a milder form of HFRS, whereas in Asia, particularly in China, Hantaan virus and Seoul virus are the frequent types that cause a severe form of HFRS [11,12].

As of now, there are no approved post-exposure therapeutic agents for hantaviral infection. The available treatment options mainly target the viral life cycle, host immunological factors or patient clinical symptoms. Inactivated whole virus vaccines, like Hantavax, are available for use in the Republic of Korea and China against HTNV or SEOV, but their efficacies have to be proved yet.

Of the various countries that have reported the hantavirus infection, China is unique as it has the highest incidence of HFRS worldwide. Almost 90% of the globally reported cases come from China [13]. The connection between China and the likely hantavirus infections can be found in 12th century literature [14]. Interestingly, the first case of clinically recognized HFRS was reported in 1931 in northeast China [3]. The Hantaan virus and the Seoul virus which are known to cause HFRS in China are carried by the striped field mice, *Apodemus agrarius*, and the Norway rat, *Rattus norvegicus*, respectively [15].

With the large number of hantavirus serotypes reported in China, it undoubtedly experiences a health care threat as far as the zoonotic diseases are concerned. Several new serotypes of hantaviruses have been identified in China in the recent past. A newly discovered hantavirus strain, designated as strain YN509, from Chinese white-bellied rats (*Niviventer confucianus*) captured in Yunnan province, China, was found to be genetically different from other rodent-borne hantaviruses in China [16]. Though the nucleotide sequences showed that the new strain is related

to Da Bie Shan virus (DBSV), which is also carried by *N. confucianus*, the phylogenetic analysis suggested it to be treated as a subtype of DBSV. As part of surveillance study of hantaviruses in rodents, Zhang and fellow researchers found a new hantavirus species in the Yunnan red-backed vole (*Eothenomys miletus*) in the HFRS-endemic region, Luxi County within the Yunnan Province of China, between 2009 and 2010 [17]. This new species was named Luxi hantavirus. Ge et al. who carried out a study among the captured animals from Fugong county, Yunnan province, China has identified a new hantavirus from a small oriental vole (*Eothenomys eleusis*) and named it as Fugong virus (FUGV) [18].

The point to note is that most of the new species/strains of hantaviruses identified in China are from the Yunnan province, where the recent hantavirus death in China is reported. Though a direct connection cannot be established, the possibility of newly emerging hantavirus species cannot be ruled out. Further details on the hantavirus death are not available, especially the hantavirus species involved and clinical complications of the victim. Though reassortment of nucleic acid segments and host switching are reported in hantaviruses from various countries, such phenomena are much more frequent in hantaviruses from rodent population of China [19].

Moreover, the high degree of genetic diversity among hantaviruses, especially among the strains isolated in China, may be attributed to the concept of spillover of hantavirus strains from one host to another host as evidenced by the spillover of Hantaanvirus from *A. agrarius* to *R. norvegicus* [20]. The role of hitherto undetected and potential hosts will be a serious issue in hantavirus epidemiology which is largely ignored in the past as quoted by Tian and Stenseth [21]. A recent article in NEJM by Morens et al., which described the mechanisms of emergence and host-switching of animal viruses, reinstated the high mutation rates of genetically error prone RNA viruses [22]. However, hantaviruses failed to find a mention in their list of zoonotic viruses which include severe acute respiratory syndrome (SARS) virus, Middle Eastern respiratory syndrome (MERS) virus, Nipah virus, arenaviruses and COVID-19. Given the fact that Hantaviruses too belong to RNA viruses and have a proven record of host-switching within the rodent populations, one must not ignore the possibility of widespread emergence of hantavirus infection. These issues further complicate the epidemiology of hantavirus infections.

Climate change has been linked to the geographic distribution, abundance, and dynamics of rodent hosts which in turn to the hantavirus infection pattern. Changes in the environment, due to increased agricultural activities and expanding human habitation, have been identified as major factors in emerging infectious diseases. These activities place

people in contact with a natural reservoir or host of zoonotic diseases often by increasing the proximity. Detailed studies on the pathogens, their vectors and the environment and the interplay between them are needed in the wake of emerging and re-emerging diseases.

The striking difference between respiratory tract infections (like COVID19) and zoonotic infections (like hantaviruses) is their mode of transmission. The chances of exposure and hence the risk of acquiring the disease are much higher in case of respiratory tract viruses as infected persons release large number of virus containing droplets. On the other hand, zoonotic viral infections often get transmitted through rodents, as in the case of hantaviruses, the chances for which is far less. Preventive measures can easily be adopted in case of zoonotic infections by controlling the rodent population at a larger scale compared to the complex procedures like self-isolation and quarantine needed to combat respiratory infections.

Surveillance measures, especially among the rodent vector population and risk groups, together with prevention and control strategies alone can prevent hantavirus infections. Although an imminent health risk at the global level can be predicted further studies in this direction will help us face a global zoonotic challenge. Studies on the transmission dynamics of hantaviruses must be prioritised to develop better prediction and prevention measures. One should not forget that the nature is the best teacher.

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