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Review

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Present and Future Implications of Crimean Congo Haemorrhagic Fever Disease Emergence in Turkey

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Abstract

Crimean-Congo haemorrhagic fever virus (CCHFV) is an emerging tick-borne zoonosis and a public health concern in Turkey since its first confirmation in 2002. The virus displays great genetic diversity and tends to expand its release to new areas. The presence of the biological tick vectors harbouring the virus and a suitable habitat are the predisposing factors for disease emergence in Turkey and elsewhere. As Turkey is one of the most endemic countries for CCHF disease, deliberate studies should be conducted to monitor all aspects of virus circulation and diversity in all endemic and non-endemic areas of the country. This will help to gain valuable information to predict the fate of the disease, and to develop effective vaccines and treatment facilities. Owing to the zoonotic nature of the virus, it offers a good prospect for collaboration of human and veterinary medicine with the view to fight the disease based on the one health initiative. This review was focussed on CCHFV diversity, perspectives of disease occurrence in Turkey, and the present and future implications of the disease.

Keywords: *Crimean Congo Haemorrhagic Fever Virus, Recombination, Reassortment, Zoonosis, Turkey*

Türkiye'de Kırım Kongo Kanamalı Ateşi Hastalığının Güncel ve Gelecekteki Etkileri

Öz

Kırım-Kongo kanamalı ateş virüsü (KKKAV), Türkiye'de 2002 yılında ilk kez tespit edilmesini takiben, halk sağlığı açısından oldukça önemli, kene kaynaklı bir zoonoz olmuştur. Etken oldukça geniş bir genetik çeşitliliğe sahip olup, gittikçe daha geniş alanlara yayılım eğilimi göstermektedir. Virüs için biyolojik kenenin varlığı ve uygun ortam şartları Türkiye'de hastalığın ortaya çıkmasında temel faktörleri oluşturmuştur. Türkiye, Kırım Kongo Kanamalı Ateş hastalığının görüldüğü en endemik ülkelerden biri olduğu için, virüs dolaşımının ve çeşitliliğinin endemik ve endemik olmayan bölgelerde ciddi araştırmalar ile sürekli izlenmesi büyük önem taşımaktadır. Bu çalışmalar hastalığın ve virüs dolaşımının gelecekteki durumunun değerlendirilmesi açısından gerekli olduğu kadar, hastalığa karşı etkili aşı ve tedavi seçeneklerinin geliştirilmesi yönlerinden de önemlidir. KKKAV, zoonotik bir etken olduğundan, insan ve veteriner tıp alanlarında Tek Sağlık yaklaşımına dayalı çalışmalar, hastalıkla savaş açısından mükemmel bir örnek oluşturmaktadır. Bu derlemede, Türkiye'de KKKAV çeşitliliği ve hastalığının ortaya çıkışı, güncel ve gelecek ile ilgili durumlar tartışılacaktır.

Anahtar sözcükler: *Kırım Kongo Hemorajik Ateş Virüsü, Rekombinasyon, Reassortment, Zoonoz, Türkiye*

INTRODUCTION

The enhancement of global trade and travel, increase in population density, environmental and climate changes are the predisposing factors for appearance of emerging diseases in the world. Many of these diseases have viral origin and display zoonotic potential and some of them have biological arthropod vectors and intermediate hosts. One of the greatest concerns about these diseases is their expansion potential to spread to different parts of the world from their place of origin [1].

Crimean-Congo haemorrhagic fever virus (CCHFV) has been classified as an emerging tick born zoonosis affecting many parts of the world. The causative agent of the disease is the RNA virus of genus Orthonairovirus, in the *Nairoviridae* family [2]. In humans, CCHFV is known to be extremely infectious and is associated with an acute haemorrhagic disease called Crimean Congo haemorrhagic fever (CCHF), with mortality rates as high as 30% [3,4]. Historically, the disease associated outbreak characterised acute febrile disease with a high incidence of bleeding and shock syndrome, which was first observed in Soviet soldiers

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during the summer of 1944, in Crimea [5]. A similar disease presentation occurred in 1956, in the Belgian Congo (Democratic Republic of Congo). In 1969, it was recognised that viruses associated with haemorrhagic syndromes in Crimea and Congo were identical and thus, the name Crimean-Congo haemorrhagic fever virus was nominated [6].

Ticks primarily belonging to the genus *Hyalomma*, play an imperative role in CCHFV survival and maintenance by acting as biological vectors. Human infection may occur either by tick bites or by contact with tissues or blood of the viremic individuals or animals in disease endemic areas. Additionally, it is thought that migratory birds and livestock trade between countries could play parts in disseminating the virus to new areas [3,4,7,8].

In comparison to other tick-borne viruses, CCHFV has been most frequently disseminated and disease cases have been documented in many countries in three continents (Africa, Asia, the Middle East and Eastern Europe) of the world [6,9]. CCHFV displays an important feature of expansion to new geographical areas, as evident by its recent emergence in Spain [10].

Disease occurrence coincides well with the presence of the tick vector *Hyalomma marginatum marginatum*. The presence of a vector tick is considered essential to establish endemic foci [3,4,11]. To date, majority of the cases have been reported in Turkey [12]. It is important to note that imported CCHF cases have also been reported in countries including France [13], Germany [14], United Kingdom [15] and Greece [16].

Owing to the lack of a prophylactic vaccine and some beneficial effect of antiviral ribavirin [17,18], an affective outbreak response depends on early confirmation of disease cases and suitable control response. In particular, the provincial health care institutions and reference laboratories play a very critical role [19]. Human infections are an extremely critical public health concern and possess the potential risk of causing nosocomial outbreaks; hence, all disease cases must be brought to the attention of public health authorities [20].

Since CCHFV infection is presented by a complex cycle that includes both human and several vertebrate host and tick vector, a collaborative action involving multiple disciplines, particularly human and veterinary medicine, based on the one health initiative is extremely important to combat the disease [21]. One health initiative to deal with this pathogen is extremely important, not only in Turkey, but also for all disease endemic and potentially endemic regions in the world.

GENETIC DIVERSITY OF CRIMEAN CONGO HAEMORRHAGIC FEVER VIRUS CIRCULATING IN THE WORLD

Crimean-Congo haemorrhagic fever virus is enveloped, spherical shaped and almost 90 nm in diameter. It harbours a single stranded and tree segmented RNA genome consisting of small (S), medium (M) and large (L) gene segments. The S segment encodes nucleocapsid protein (NP) with endonuclease activity [22-24]. The M segment encodes a glycoprotein precursor that undergoes post-translational cleavage to give rise to two structural glycoproteins (Gn- 37 kDa and Gc- 75 kDa) and three non-structural proteins (NS_M, mucin-like domain and GP38). It is important to note that M segment is the most variable, as compared to S and L segments [23-26]. Glycoproteins Gn and Gc are responsible for virus attachment to host cells and contain epitopes for eliciting neutralising antibody response [27-30]. The L segment encodes L protein displaying viral RNA-dependent RNA polymerase activity [4].

In comparison to other arboviruses, CCHFVs display a wide genetic diversity as evident in the phylogenetic analyses. The diversity of CCHFV is related to the recombination and reassortment events that inevitably occur in the segmented RNA genome [6,31-33]. Recombination events are suggested to occur between the S segments of local topotype viruses circulating in Turkey [34]. In addition to recombination event(s), reassortment events have been observed, primarily in the M segments. Phylogenetic studies based on M segment sequences differ from those based on S and L segment sequences, as reassortment often occurs by chances in the M segments of viruses [6,7]. Reassortment events associated with M segment may result in the generation of novel isolates with enhanced virulence. Thus, studies of M segment variations are of critical importance to evaluate viral virulence mechanisms attributed to respective isolates [28,30,33].

The high genetic diversity observed in the CCHFVs circulating in the world has led to the classification of viruses in genetic groups or genetic lineages. Phylo-genetic analysis of CCHFVs based on mostly partial and more limited number of whole gene segments of viruses have shown that the viruses are classified into seven genetic lineages or groups in association with geographical regions. These include Africa 3 (South Africa, Iran, Mauritania, Senegal) Africa 2 (South Africa, Democratic Republic of Congo, Uganda, Namibia), Africa 1 (South Africa, Namibia, United Arab Emirates, Senegal, Mauritania, Nigeria, Burkina, Faso), Asia 1 and Asia 2 (Iran, Pakistan, United Arab Emirates, Madagascar, Oman, Iraq, China, Uzbekistan, Tajikistan, Kazakhstan), Europe 1 (Turkey, Russia, Greece, Kosovo, Bulgaria, Albania, Iran), and Europe 2 (Greece, Turkey) [6,31,33,35,36]. In addition, it was reported that two isolates characterised by whole genome analysis in China were formed as an independent group with reference viruses in phylogenetic analysis [37].

Phylogenetic studies involving CCHFVs across the world suggest that the ancestor of all genetic lineages emerged approximately a few thousand years ago, probably in Africa [35,38]. It is thought that the virus first reached south and central Asia during the middle ages and then, spread

to China, India, and Russia. Viruses belonging to European I lineage reached south Russia from Astrakhan 280-400 years ago and in less than 150 years extended from Russia to Turkey and Balkans [38].

EMERGENCE OF CRIMEAN CONGO HAEMORRHAGIC FEVER DISEASE IN TURKEY

The emergence of CCHF disease was first recognised in the Tokat province in the Kelkit Valley in northern part of Turkey in 2002 [39,40]. Since 2002, CCHF disease reports have increased and expanded to occur in several provinces in Kelkit Valley, which has been the endemic region for the disease. Between 2002 and 2017, a total of 10.562 confirmed cases and 501 deaths were recorded by the Turkish Ministry of Health (http://www.thsk.gov.tr). In general, the mean mortality rate is around 5% in Turkey [18,41].

Since the first confirmation of the disease in 2002, the majority of cases have been reported from the north of middle Anatolia and Black Sea region, having similar climate and environment conditions, especially from the provinces of Tokat, Yozgat, Sivas, Gumushane, Artvin, Bayburt, Erzurum, Erzincan, Amasya, Cankiri, Corum, Kastamonu [12,40,42]. It is assumed that the emergence and increase in disease incidence are facilitated by multiple predisposing factors associated with disease endemic regions including climate change as well as anthropogenic factors such as changes in agricultural habits and increase in wildlife population. In particular, the climate change along with anthropogenic factors may have caused significant effect on reproduction rate of *Hyalomma* tick. This inevitably resulted in extensive amplification of virus through tick vertebra tick cycle (along with increase of wildlife population) [20,43-45]. Owing to security reasons, several activities including, agriculture, farming, and hunting were limited in the rural areas in Tokat and neighbouring provinces between 1995 and 2001. In particular, the restriction of hunting probably resulted in increased wild animal population such as wild boars, hares, and other animals that served as amplifying hosts for virus. After the re-opening of these areas for use, people and livestock such as cattle and sheep might have been exposed to a large number of *Hyalomma marginatum marginatum* ticks, resulting in disease emergence [12]. Importantly, a high landscape fragmentation and warm climate conditions are optimal habitats for the vector, *Hyalomma* ticks, and coincide well with the high disease risk areas in Turkey [43]. It is very likely that potential factors contribute to disease emergence in Turkey, and may also be attributed to emergence of disease in Crimea, Bulgaria, Albania, and Kosovo [9,43,46,47]. In the previous years, CCHF cases were usually reported between April and September, with the highest number of cases in July, in Turkey. Recently, the case report period has been extended from March to November [44].

Tick bites are considered to be the most common route of CCHFV infection in Turkey [9,12,41]. Approximately, two thirds of CCHF disease cases have been reported among farmers and home makers in disease endemic areas and these people were probably exposed to vector ticks during their daily life [44].

Despite the lack of the CCHF disease report before 2002, it was very likely that the virus had been circulating in enzootic vertebrate tick vertebrate cycle in nature. In particular, some studies indicated the detection of virus specific antibodies among individuals in some parts of country suggesting virus circulation prior to disease emergence [44]. A survey carried out by Bodur et al.[48] in 2009 indicated that seroprevalence of CCHFV infection was 10% in disease endemic area. Their survey also reported the increase of the seropositivity with older age and presence of subclinical infections. In another survey, seropevalence was found to be 12.8% in disease endemic areas [42]. Koksal et al.[49] reported that seroprevalence was 13.6 in relatives and close neighbours of CCHFV infected patients, as a result of possible exposure of the virus. Epidemiological studies are undoubtedly indicative of virus circulation and subclinical infections prior to disease emergence in Turkey.

It is known that migratory birds harbouring infected ticks could play a role in introducing the virus to new areas [8]. Anatolian peninsula is located on the Black Sea and Mediterranean flyway of migratory birds. The presence of CCHFV infected nymph on migratory birds was detected by a study carried out by Leblebicioglu et al.[50]. Phylogenetic analysis revealed that viruses carried by migratory birds are closely related to European-Russian viruses belonging to European lineage I. It may be assumed that the migratory birds from which infected ticks were recovered, such as the great reed warbler, have the potential to move to Russia, Turkey, Europa, Africa and North Africa and the European robin can migrate to Russia, Turkey, Europa, and North Africa. Thus, it is not unlikely that migratory birds carrying infected ticks may contribute to further outbreaks [12].

Livestock trade and/or movements may also lead to CCHFV introduction in countries, through infected ticks. CCHF disease is also common in a neighbouring country, Iran, but studies indicated that viruses belonging to different genetic lineages were circulating in Iran [34,51]. A study conducted to characterise CCHFVs obtained from ticks on small ruminants near Turkish border in Iran revealed that the viruses belonged to European lineage I and displayed phylogenetic similarity with viruses characterised from human cases in Turkey. This is suggestive of transborder CCHFV transmission between these countries [52].

Owing to the extremely infectious nature of the virus, human infections possess the potential risk of causing nosocomial outbreaks and transmission of the disease to health care professionals [20]. A majority of nosocomial infections have been acquired while dealing with CCHFV

patients [9,53]. Transmission of CCHFV to health care workers has been occured in Turkey, and some cases, resulted in the fatal outcome [12].

PHYLOGENETIC ANALYSIS OF CRIMEAN CONGO HAEMORRHAGIC FEVER VIRUSES CIRCULATING IN TURKEY

In Turkey, phylogenetic studies mostly based on partial S, M and L segment sequences of CCHFV isolates derived from infected individuals and ticks revealed that a majority of isolates belonged to the European lineage I, including viruses characterised in Eastern Europe and Balkan Peninsula [28,29,34,54-56]. Kalaycioglu et al.[54] and Kalaycioglu et al.[55] reported two studies on molecular characterisation of CCHFVs harvested from infected individuals in disease endemic areas, between 2009-2012, in Turkey. Their study confirmed that the circulating viruses belonged to European lineage I, including viruses characterised previously in Turkey. Importantly, Kalaycioglu's studies agreed with the circulation of closely related viruses called local topotype as suggested by Ozkaya et al.[34].

The existence of AP92-like viruses that was first isolated from *Rhicephalus bursa* ticks in 1975 in Greece and classified within European lineage II were also detected in Thrace region (European part) of Turkey [57,58]. In particular, Gargılı et al.[58] reported the co-circulation of strains belonging to European I and European II lineages among ticks in the European part of Turkey. A recent study based on surveying the tick-borne viruses in Turkey showed that AP92-like viruses were found to be circulating in areas spanning the south and eastern Anatolia regions [59]. Although this group of viruses was initially thought to be non-virulent for humans, some mild clinical cases associated with AP92-like viruses were reported in rural Balkanian (Thrace) part of Istanbul [57,60] and Corum province located in central Anatolia region in Turkey [34]. Importantly, an AP92-like viral RNA was detected in a case, resulting in death in 2015, in Iran [61]. This suggests that there may be possible virulence differences between AP92-like strains, resulting in serious disease conditions. This possibility needs to be further investigated by case-based surveillance studies using whole genome sequence analysis of respective isolates.

FUTURE PATTERNS OF CRIMEAN CONGO HAEMORRHAGIC FEVER DISEASE IN TURKEY

Molecular insights for possible virus introduction belonging to different lineages: The circulation of viruses from different genetic lineages in the same regions suggests the potential of the viruses to spread through migratory birds and/or trade of farm animals between countries [8]. This situation is critically important in terms of the ability of viruses from different genetic groups to circulate in a region and to infect the ticks and provide a suitable environment for ressortment [6,33].

The reassortment events were reported between and south and west African isolates and between Asian and southern African isolates of CCHFVs. It is interesting to note that the reassortments between west African and southern African viruses were associated with the L segment, while reassortment events between southern African and Asian isolates were associated with the M segment of the RNA genome [33].

A study carried out by Deyde et al.[31] suggested potential reassortment events between Turkish (200310849) and Russian (Kashmanov and Drosdov) strains. In their study, the phylogenetic analysis of M segment sequences of these viruses displayed a close relationship and clustered in European I genetic lineage while Drosdov and Kashmanov strains formed closely associated groups in phylogenetic analysis based on the S and L segments. Another recent study conducted by Lukashev et al.[38] also suggested possible reassortment events between European lineage I viruses.

The M-segment coding for glycoproteins is essential for binding to host cell receptors and also harbours neutralizing epitopes. These features make the M segment associated genetic variations and especially reassortment events more critical. In particular, reassortment events related to the M segment may lead to generation of viruses with an increased virulence [28,32,33]. In this respect, the viruses being circulated in any part of the world and importantly in Turkey need to be constantly monitored and followed up by molecular analyses.

Due to the expansion tendency of CCHFVs, Turkey may not only be considered as a "donor" country for Europe [8] but also as a ''recipient" of new virus isolates from neighbouring countries such as Eastern Europe and particularly from Iran [54,55]. It was determined that viruses belonging to Asia I lineage were common in Iran and its neighbouring country Iraq, and the circulation of Asia II lineage viruses was also detected [62,63]. In addition, the presence of viruses belonging to European lineage I, and European lineage II viruses as a new genetic group have also been detected in Iran [62,64,65]. Interestingly, phylogenetic analysis of CCHFVs obtained in ticks collected from small ruminants in Southwestern region of Iran showed that viruses belonged to European lineage I, which was similar to viruses characterised in Turkey. This highlights the possibility of virus introduction between neighbouring countries by livestock trade and/or movement [52].

Turkey is located on the migratory routes of birds and has borders with Balkan and Middle Eastern countries. Therefore, it is not unlikely that viruses in different

genetic lineages may participate in circulation. This could facilitate reassortment event(s) between CCHFVs and the generation of reassortant viruses. In order to investigate the presence of viruses with different genetic lineage and possible genetic variations between viruses circulating in Turkey, it is essential to carry out molecular analyses based on whole genome sequences of CCHFVs. Whole genome-based characterisation studies involving Turkish isolates will provide invaluable insights to define constant and variable segments of the genome. This would also contribute significantly to antivirals and vaccine development studies.

CRIMEAN CONGO HAEMORRHAGIC FEVER OUTBREAK RISKS IN NON-ENDEMIC AND POTENTIALLY ENDEMIC PARTS IN TURKEY

The expansion potential of the CCHFVs and their tendency to establish new niches is not only critical for the world, but also important for Turkey. A study carried out by Tuncer et al.[66] reported 33.1% CCHFV antibody prevalence in livestock, in parts of South Marmara region of Turkey. A tick survey carried out by Yesilbag et al.[67] also confirmed the existence of CCHFV circulation in the same region. Two CCHF disease cases were confirmed in Bursa and Canakkale provinces of South Marmara region in Turkey [68]. Importantly, an outbreak and human infections were reported in Aydın province located in Aegean region of Western Anatolia [69]. Seroprevalence studies using human sera obtained from volunteers indicated that seropositivity were 19.6 and 19.7 in potentially endemic and non-endemic parts of Aydın province, respectively [70,71]. The presence of CCHFV antibodies in livestock, wild animals, and occurrence of disease cases in non-endemic parts of the country highlight the widespread distribution potential of CCHFV. Importantly, this was indicative of the presence of potential endemic regions in addition to Kelkit Valley in Turkey. Thus, further research regarding detection of CCHFV circulation in ticks, wild animals and livestock is essential to define all disease potential areas in Turkey. Potential predisposing factors could initiate new outbreaks in non-endemic areas. Therefore, precautions and public awareness has to be taken to minimise future outbreaks in Turkey.

PUBLIC HEALTH CONCERN OF CCHF DISEASE DURING EID-AL-ADHA

One of the most important public health aspects of CCHFV is its potential to cause disease cases and outbreaks during the time of Eid-Al-Adha. Thousands of livestock are transferred, and many people are involved in sacrificing activity nearly in every province of Turkey. In fact, CCHF disease outbreaks have been reported during this religious time in Pakistan [72]. According to the early drift of 10-11 days every year, this period will lie during summer and spring months for the next 10-15 years, when the vector ticks are active and prevalent [12]. This will not only be an important health concern for people in endemic areas but also for people residing in non-endemic parts of the country. In particular, the transport of livestock will definitely lead to transfer of infected vector ticks and viremic animals from endemic areas [73]. This will enhance the risk of transmission of CCHFV to humans. Hence, veterinary control for animal movements and training of staff involving animal sacrificing procedures is essential and all necessary precautions are imperative to minimise the risk of virus transmission.

ONE HEALTH INITIATIVE TO COMBAT CCHF DISEASE

Since CCHFV possesses a zoonotic behaviour, it is an excellent subject to establish a one health initiative-based campaign, which requires multidisciplinary collaborative studies including human and veterinary medicine and other related disciplines. Because of the lack of the effective prophylactic vaccine and limited treatment facilities, it is essential to implement all possible protective measures to prevent and control future outbreaks [21]. Implementation of one health disease surveillance and interdisciplinary actions investigating circulation of CCHFVs in ticks, wild animals and livestock by well-designed molecular epidemiologic studies in both disease endemic and potentially endemic areas in Turkey will lead to quicker disease recognition, efficient outbreak response and disease control.

The detection of virus specific antibodies is an important mediator to detect the presence and circulation of virus, which should be combined with tick based studies to evaluate the risk of future outbreaks in any potential area. This is particularly important to map areas where outbreaks could occur in future and to alert public health systems. If the prevalence of CCHFV increases in ticks, in conjunction with virus specific antibody circulation in wild and domestic animals in any given area, cases of disease outbreak may occur [9,44,45]. These examples highlight the importance of veterinary medicine in the one health initiative, particularly in case of CCHFV disease.

CONCLUSION

Since CCHF disease has been an important public health priority in Turkey, the disease surveillance is a fundamental issue for public health actions to detect, prevent and respond to health threats effectively in time. Early diagnosis of disease and all preventive measures are essential to minimise disease related disorders. One health initiative is the most ideal way to deal with CCHF disease and its public health consequences.

The existence of high genetic diversity in CCHFV strains

has resulted in the generation of different genetic lineages, distributed in various disease reported regions. The investigation of possible co-circulation of virus strains that belong to different lineages is a critical issue for CCHFV research in Turkey. This issue can be addressed by whole genome sequence analysis of isolates derived from ticks and infected individuals. The whole viral genome characterisation studies including viruses detected in Turkey are also imperative to gain valuable results and essential for vaccine and antiviral development.

Turkey's considerable experiences and efforts to deal with this tick-borne zoonosis have been a beacon for other disease endemic countries and also to countries that are at risk of being endemic in the future.

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