ALKHUMRA HEMORRHAGIC FEVER VIRUS (AHFV): CURRENT STATUS AND FUTURE PROSPECTS

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Submitted in December 2021, accepted in October 2022

Abstract: The objective of this review to summarize the current status of information about the Alkhumra hemorrhagic fever caused by Alkhumra hemorrhagic fever virus an Arboviral infection. This virus was identified in Alkhumra district of Jeddah, Saudi Arabia in 1995 from a butcher patient. The infected individual develops symptoms febrile flu-like illness, hemorrhagic manifestations and less like encephalitis. Several cases have been reported from various locations of Saudi Arabia and a few from Egypt and is further expanding in tropical and subtropical regions of Western Asia. The virus is transmitted to human by direct contact to animal, raw meat, and biproducts as well as either tick or mosquito bites. Based on the recent status, a great concern of public health was raised with the AHFV epidemics and infection. Currently, there is no effective vaccine and antiviral therapeutics against AHFV. So, there is an urgent need to design and develop an effective preventive measure using interdisciplinary approach. This review will provide the status of research work based on the latest published information about AHFV. The provided information will be highly useful to design the effective preventive measures to control the disease in the Kingdom of Saudi Arabia.


Keywords: AHFV, Alkhumra, diagnosis, prevention and management, transmission

1. Introduction

A new viral disease known as Alkhumra hemorrhagic fever caused by Alkhumra hemorrhagic fever virus (AHFV) was reported from the Alkhumra, Jeddah, Kingdom of Saudi Arabia in 1995 [27]. Later, the causative agent was identified and characterized and was designated as “Alkhumra hemorrhagic fever virus” (AHFV) based on the first case of identification from Alkhumra district [11, 30]. The AHFV belongs to the Flaviviridae family with ss positive sense RNA. Based on current status few clinical cases of this virus has also been reported from Makkah (20 cases), Najran (8 cases), and bordering Yemen (70 cases) Taif, Alqunfuda and Jazan [2, 17, 22]. The was isolated as well from different hosts in Egypt, Italy [4, 23, 28] and Djibouti [3, 8]. These reports warrants to an alarming situation and suggesting the expansion of geographic distribution beyond the origin. The emergence and re-emergence of AHFV has significant impact on human and animal health.

2. Molecular characterization

The molecular characterization of AHFV has been done by many research groups. Like other Flaviviruses, AHFV genome size ranges from 10.5 to 10.7 kb and codes a polyprotein which cleaves into structural and non-structural proteins (Coat, Pre- Membrane and Envelop- Structural proteins) and non-structural protein known as NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 by viral and host proteases [1, 9, 10, 12, 18, 19, 24, 26, 29]. The 5’ and 3’ untranslated regions (UTRs), of the viral genome consist the coding sequence responsible for viral pathogenicity. The trypsin-like serine
protease and helicase domains are localized on NS3 region and methyl transferase and RNA-dependent RNA polymerase domains are present on NS5 region. The NS2B works as a cofactor for protease activity of NS3 [24, 25]. The first report about full genome sequencing and analysis of AHFV strain 1176 which was identified from an infected patient was published by Charrel et al in 2001. The complete genome had 10248 nucleotides with 3416 amino acids polyprotein [7]. Based on the genetic characterization relationship, Kyasanur forest disease virus (KFDV) showed the closest cluster, and it was likely to be the common ancestor and represent two genetic subtypes of the same virus species. Additionally, the sequence analysis of 11 AHFV isolates collected from Makkah and Jeddah as well as one isolate from Ornithodoros savignyi tick, sand tampan (tick JE7), showed the sequences similarity with AHFV strain 1176 and KFDV especially in the envelop protein gene but less similarity was observed in NS3 and NS5 gene which indicates low microevolution [5, 6]. In 2014, another full genome sequencing and analysis of AHFV strain isolated from Najran was performed by Madani et al and the results showed the AHFV-Najran strain had 10546 nucleotides as compared to other strains had 10,685–10,749. The sequence similarity showed 99% identity to other 18 AHFV strains and the phylogenetic relationship showed the AHFV formed closed cluster with previously reported AHFV strains while KFDV, Langat virus, TBEV, and OHFV isolates formed a separate cluster. This sequence analysis concluded that the AHFV-Najran strain could have resulted from possible recombination with circulating strains in Saudi Arabia [18].

3. Transmission of AHFV

The possible mode of transmission of AHFV has been reported in many studies. The direct contact with animals and their by products such as raw milk, raw meat, secretions and blood, and exposure to ticks and plays an important role in transmission [11, 22, 27, 30]. But there were several reports suggest that mosquito bites can also play important role because some affected patients were not in the direct contact with animals and their bi-products. Tick and tick bites may be suspected as the reservoir and possible source of virus spread to humans [11, 17, 20]. But in another study, a significant risk factors of AHFV infection are possible after multivariate modeling, animal contact, neighboring farms, and tick bites [2]. The human-to-human transmission of AHFV has not been reported but based on some reports 32.1–71.4% cases were the part of same family cluster [2, 17]. In an interesting study, it was observed that the successful propagation of AHFV in mosquito cell lines and based on this study it may be hypothesized that mosquito could be an important vector for virus transmission [14, 16, 20].

4. Diagnosis and Sero-surveillance of AHFV

The laboratory diagnosis of AHFV infection can be performed by both standard serological and molecular techniques [17, 30]. The AHFV can be detected with immunofluorescence assay (IFA) by using the flavivirus-specific monoclonal antibody 4G2. Additionally, NS5 gene specific PCR also successfully detect the AHFV infection and provides the 220 bp amplicon. The detection of AHFV by Realtime-PCR is more sensitive than viral culture and it has been shown by the detection of virus in serum, plasma, and theuffy coat [13, 15]. Serosurveillance data on AHFV antibodies in humans in the KSA or elsewhere are scarce. The study report suggests that the prevalence of AHFV-IgG was 1.3% among 1024 soldiers from different regions of the KSA [21]. The positive sera in different locality such as Tabouk (61.5%), 23.1% from the Eastern region, 7.7% from Asir and Jazan (7.7%). In an interesting study, it was observed that the individuals were AHFV- IgG positive and there were no reported cases of AHFV in their locality in the past and this suggests that they may had mild infection earlier with AHFV.

5. Clinical features, mortality of AHFV infection and manifestations

The first case of AHFV was detected in Alkhumra district and total 37 suspected cases were notified in 2001–2003. The clinical features of ALKV is extremely severe. Only 20 cases were confirmed by laboratory diagnosis and 11 have hemorrhagic manifestations and finally 5 of them died confirming the high (up to 30%) case fatality rate which reflects that the ALKV is the deadliest virus [2]. The frequency of multiple features including clinical, and laboratory have been described in the outbreak occurred in Jeddah, Makkah and Najran [2, 4, 11, 17, 22]. The clinical manifestations range from mild to severe and includes fever, headache, retro-orbital pain, arthralgia, myalgia, anorexia, vomiting, leukopenia, thrombocytopenia, and elevated liver enzymes, creatine kinase, and lactate dehydrogenase. Additionally, gastroenteritis-like illness, rhabdomyolysis, severe muscle weakness and as well as severe neurologic and hemorrhagic symptoms have also been reported [1, 22, 28]. The mortality rate of AHFV infection ranged from 20–30% in Jeddah and Makkah [11, 30]. But based on the recent outbreak in Najran (2003–2009), Taif, Jazan (2010–2015), and in Algun-
fuda in April 2017, the mortality rate was ranged from (<0.5–1%) [2, 11, 17, 22, 30]. The rate of low mortality in these regions suggests that the protective herd immunity among the inhabitants has been developed against this virus [17].

6. Prevention control and management of AHFV

As per latest published information and epidemiological data, the livestock animal, tick and mosquito bites play an important role in the possible transmission of AHFV in both human and animals. Currently, there is no specific vaccines and antiviral therapy to control and manage the AHFV infection. The effective patient supportive care with intravenous fluids, ionotropic support, blood and fresh frozen plasma transfusions and mechanical ventilation suggests the proper control and management of virus infection. The infection of AHFV can be prevented by the direct contact with these animals and their biproducts as well as avoidance of mosquito and tick bites. The immediate information should be provided to Health and agriculture ministry about the virus infection and risk factors in a particular locations and municipality animal handlers, slaughterhouses, and workers. The preventive measures should be taken by all the workers, and they should protect themselves by using personal protective equipment during handling of their animals and biproducts. The control measure of mosquito bites and ticks should be undertaken by concerned ministries and authorities. A national program for controlling the ticks and mosquitoes should be established. The assessment of clinical manifestations in livestock animals as well as animal handlers should also be frequently performed to control the virus spread. The continuous collection of fecal, urine and blood samples and their proper storage should be performed so that the presence of virus and neutralizing antibodies can be detected by both serological and molecular techniques. The interdisciplinary teamwork should also be performed by including health ministry, agriculture ministry, municipality manager, slaughterhouse in charge and vector control authorities of Kingdom of Saudi Arabia.

7. Conclusion and future prospects

Based on the status and published reports, there is no effective vaccine and therapy available for AHFV infection in the Kingdom of Saudi Arabia. This virus was reported from Jeddah in 1995 and not much work has been done about the virus disease spread, vectors (Ticks and mosquitos), virus reservoir, emergence and re-emergence, virus genetic diversity, recombination, factors of virus and disease spread as well as pathologi- cal and clinical manifestations. To date there is no established reports and study about the virus hosts, their bi-products, and their role in virus transmission and maintenance even though the virus has been detected from various hosts and ticks. The role of vectors in virus disease spread to human and animals needs to be elucidated in research studies including biological role; epidemiology, seroprevalence of AHFV antibodies in both human and animals and transmission of the virus. An effective preventive measure should be taken by involving both human and veterinary sectors, manager of slaughterhouses, ministry of Agriculture, ministry of health. Additionally, the research and academic institutes should also be included so that an effective vaccines and antiviral therapies can be designed and developed to control and manage the AHFV disease in the Kingdom of Saudi Arabia.

References