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REVIEW

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Alkhumra Hemorrhagic Fever Virus (AHFV): A Concise Overview

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Alkhumra fever is a viral disease caused by the Alkhumra hemorrhagic fever virus (AHFV). It belongs to family *Flaviviridae*, genus *Flavivirus*. AHFV is primarily transmitted to humans through the bite of infected ticks, for example, *Hyalomma*. This disease was first identified in the Kingdom of Saudi Arabia (KSA) in 1995 and then reported in other countries of the Arabian Peninsula and the Middle East. The AHFV genome consists of a positive-sense, single-stranded RNA molecule of approximately 10.2 kilobases (kb) in length. The Open Reading Frame (ORF) encodes a polyprotein precursor that is processed by viral and host proteases to yield individual viral proteins. The polyprotein precursor is cleaved by viral proteases and host signal peptidases into three structural and seven non-structural proteins. AHFV can cause a range of clinical manifestations, from mild flu-like symptoms to severe hemorrhagic fever. In this review, we focus on insightful understanding of molecular biology, pathogenesis, and their potential therapeutic targets for AHFV.

INTRODUCTION

Alkhumra fever is a viral disease caused by the Alkhumra hemorrhagic fever virus (AHFV). It was first reported as hemorrhagic fever in the Kingdom of Saudi Arabia (KSA) in 1995 [1-3]. The virus was recognized as AHFV and belongs to the family *Flaviviridae* [4,5]. The term "Alkhumra" was derived from the name of the place where the first case was reported, ie, Alkhumra, a district in Jeddah, Saudi Arabia; therefore, it was called "Alkhumra Hemorrhagic Fever Virus" [5-7]. Almost 20 people with AHFV infection were found in Mekkah and later the Najran area of southern Saudi Arabia between 2001 and 2003. Later on, around 2003 and 2007, eight new instances of AHFV infection were recorded from the Najran area (See Figure 1) [8-10]. Thereafter, a rapid surge in infection from this region was observed, with 70 cases in 2008-09 [9,11]. Places like Jeddah, Makkah, and Najran

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Abbreviations: AHFW, Alkhumra Hemorrhagic Fever Virus; Kb, kilobases; KSA, Kingdom of Saudi Arabia; KFDV, Kyasanur Forest Disease Virus; ICTV, International Committee on Taxonomy of Viruses; ORF, Open Reading Frame; Nt, nucleotide; UTRs, untranslated regions; TBEV, Tick-Borne Encephalitis Virus; IFA, Immune-fluorescence assay; RT-PCR, Real-time PCR.

Keywords: Alkhumra hemorrhagic fever virus, *Flaviviridae*, Kyasanur Forest disease virus, *Ornithodoros Savignyi*

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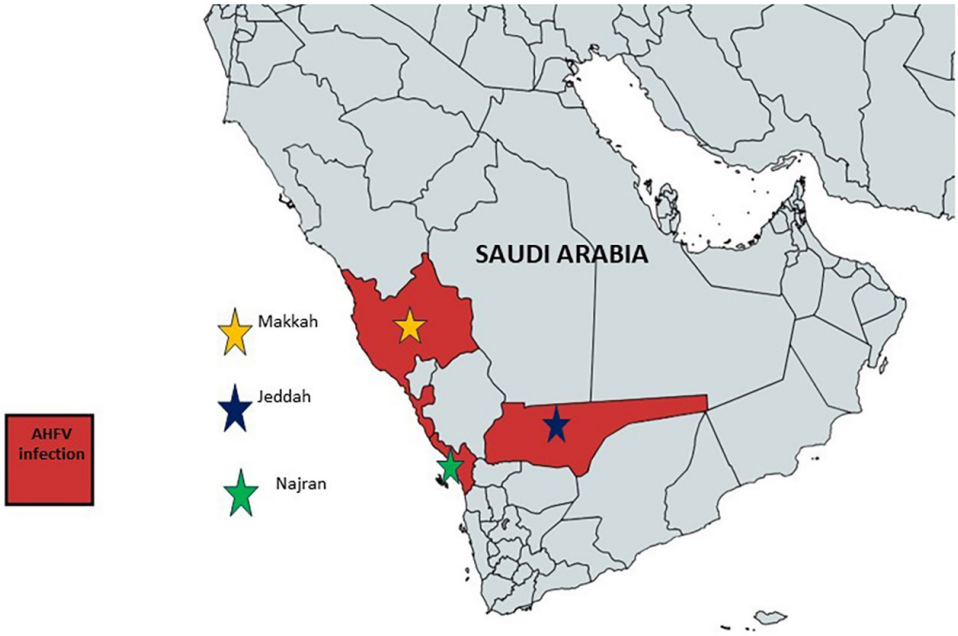

Figure 1. **Map showing major cities of Saudi Arabia with AHFV infection**.

became the most vulnerable regions for AHFV infection. This viral infection further reached to southwestern areas, including new locations like Taif, Alqunfuda, and Jazan, they also showed sporadic cases in subsequent years [10]. The AHFV infection kept spreading and reached Italy when two Italian travelers were found infected on their return journey from southern Egypt [12-14]. Following that, two additional Italian visitors were determined to be afflicted with AHFV. These patients' travel records revealed that they had recently returned from Egypt. In 2011, another sero-surveillance study revealed the presence of antibodies against AHFV in a female child of 13 years residing near a slaughterhouse in Djibouti; it was the first study about the existence of AHFV antibodies [15]. Later on, in Djibouti, cattle were found infected with AHFV along with ticks in 2010-11 [16].

Severe AHFV infection causes hazardous consequences such as severe hemorrhagic disorders, which can lead to death [17-19]. AHFV genome study indicated that it is a distant form of Kyasanur Forest Disease Virus (KFDV), which is widespread in Karnataka, India [20,21]. From 2004-05, samples of sand tampan ticks (*Ornithodoros savignyi*) isolated from camel shelters and camels were determined to be positive for AHFV using the reverse transcription-PCR technique [22,23]. Ultimately, AHFV was recognized as a zoonotic disease and their hosts were recognized as livestock animals of arid regions like camels, sheep, etc. The most common ways to spread this virus is via contact with skin or exposure of a wound to the blood of an infected animal. It can also be transferred via a tick bite, contaminated raw milk, or directly from infected items [24-30].

EPIDEMIOLOGY AND ITS GEOGRAPHICAL DISTRIBUTION

Summer and wet seasons are the most common times for AHFV infection [29]. The breeding, growth, and development of ticks and mosquitoes (arthropod vectors) during summer and rainy seasons are the optimal conditions. There is a pattern of resemblance between AHFV peak eruption and climatic circumstances (summer and rainy seasons) for other arboviral illnesses and AHFV infections, which enhances vector-host interactions. The most susceptible cohort for AHFV infection is between the ages of 10 and 40, accounting for around 80% of cases [10,24,26,29]. Younger children under the age of 10 are less likely to be infected with AHFV [8-31]. The clinical statistics of AHFV infections from Najran and Makkah were nearly identical [32]. The primary difference between the Najran and Makkah infections were as follows: first, a significant proportion of females had this infection (38% versus 10%), second, an increased number of children who contracted AHFV infection were almost 10 years old (five patients versus none), third, patients with infected family members having AHFV-like illness (25% versus 5%), and finally, lower mortality (1.3% versus 25%) was observed in Najran. These were the primary variations seen as a result of different lifestyle modifications in these places.

In the extended families of Najran (rural), people live together in big houses with backyard gardens used

Table 1. Comparison of Characteristics of AHFV and KFDV

Characteristic	AHFV	KFDV
Discovered in year	1995	1957
Genus	*Flavivirus*	*Flavivirus*
Reservoir	Unknown	Monkey
Vector	Unknown	Ticks
Transmission	Direct contact of contaminated blood and any products of infected livestock animals or tick bites or may be mosquito bites	*Haemaphysalis* tick bites that have contact with monkeys
Ecosystem	Arid regions (urban and rural)	Forest
Geographic distribution	South of Saudi Arabia, south of Egypt, and some African countries	Endemic to Southern part of India (first of reported from the Kyasanur Forest of Karnataka)
Incubation period (Days)	Unknown	2-8
Fatality rate	Less than 1-25%	3-10%
Diagnosis	PCR and Virus isolate sequencing	PCR and Virus isolate sequencing
Serological identification	ELISA and other test like serum neutralization	ELISA and other test like serum neutralization
Treatment	Treatment unknown and supportive care	Treatment unknown and supportive care
Vaccine	Not available	Vaccine used in endemic areas of India
Way to prevent and avoid infection and its transmission	• Ignore direct contact of infected livestock animals and their products. • Wearing personal protective accessories like gloves, apron etc. whenever coming in contact with infected animal or their products having this virus infection. • Apply tick and mosquito repellant cream or spray. • Use of mosquito net and avoid living under trees. • In endemic situations, take high precaution to avoid of contact with ticks and mosquitoes.	• Control of ticks. • Wearing personal protective accessories like gloves, apron etc. whenever coming in contact with infected animal or their products having this virus infection. • Avoid contact with mammals like monkeys.

as shelters for livestock animals. The majority of affected family members, including women and children, work in livestock feeding, milking, slaughtering, and butchering. The exceptionally low mortality from AHFV in the Najran outbreak appears to be attributable to AHFV epidemicity establishing in such areas. This might be the result of repetitive viral exposure, which leads to the establishment of herd immunity.

AHFV CLASSIFICATION

The AHFV is a tick (an arthropod) borne hemorrhagic disease. The causative agent of AHFV is from family *Flaviviridae*, and the genus *Flavivirus* [1,3,33-35]. AHFV is very similar to KFDV in several ways, like genetics, mode of transmission, etc. The name of this virus was originally a typographical mistake. Several publications incorrectly wrote "ALKHUMRA" virus as "ALKHURMA" which was a typographical error [33-35]. In 2011, the International Committee on Taxonomy of Viruses (ICTV) approved and corrected its name to "ALKHUMRA" [36]. However, still, some authors are using the incorrect name that is "ALKHURMA" in their publications [37-39]. A comparative characteristic of AHFV and KFDV is summarized in Table 1.

MOLECULAR CHARACTERISTICS OF AHFV

The complete ORF (open reading frame) was isolated from the blood of an AHFV-infected patient in 1995 [40-43] and is comprised of a single positive-sense RNA. The whole viral genome sequence is 10 248 nucleotides (nt) in length that has a single ORF meant for coding a polyprotein, having 3416 amino-acids [44]. AHFV genome encodes a polyprotein for structural and non-structural

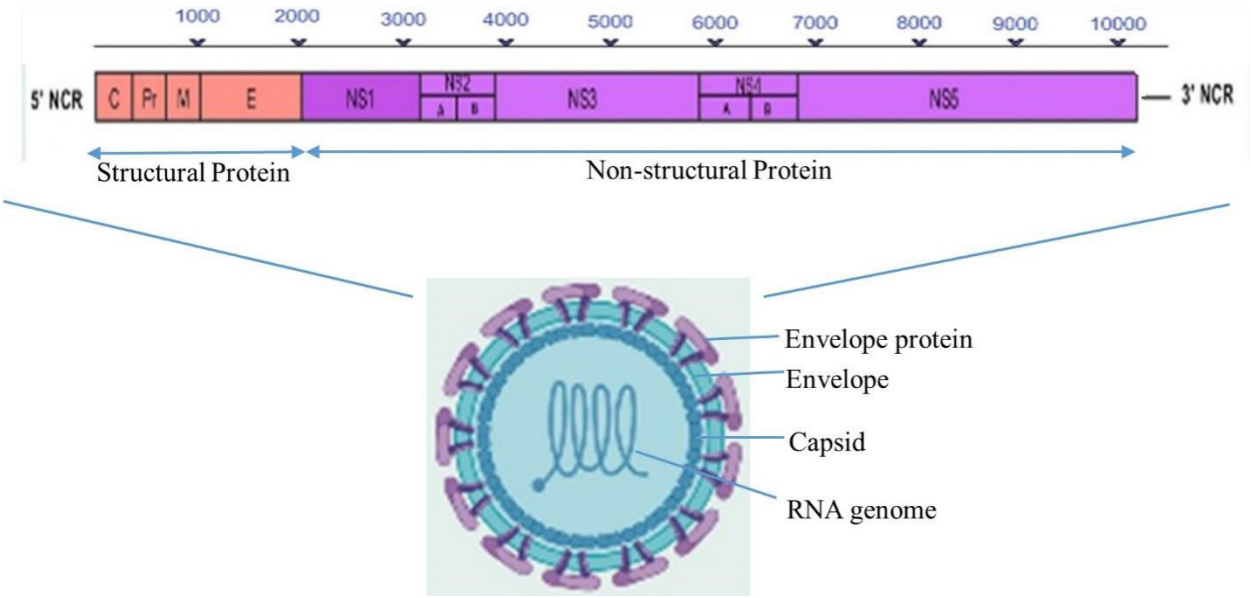

Figure 2. **The AHFV genomes open reading frames, structural, and none-structural viral proteins**.

genes (structural proteins: coat, pre-membrane, and envelope proteins, and non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5; see Figure 2). The viral genome contains a coding sequence that is responsible for viral pathogenicity in the 5' and 3' untranslated regions (UTRs). The NS3 region contains protease and helicase domains, whereas the NS5 area contains methyl transferase and RNA-dependent RNA polymerase domains. The NS2B domain acts as a cofactor having protease activity of NS3 [44,45].

Molecular studies of envelope protein and structural genes, evolutionary relationships, and phylogenetic analysis of these polypeptides revealed that AHFV was related to a tick-borne *Flavivirus* group. Additionally, an independent study showed that there was a close relation between AHFV and KFDV [46]. It was reported that both AHFV and KFDV showed the same lineage with two genetic subtypes. Between 1994-99, studies on the hospitalized patient's sample of AHFV in Makkah and Jeddah (KSA) showed low diversity and slow microevolution of partial envelope, NS3, and NS5 gene sequences for each isolate. The ancient lineages of AHFV and KFDV have shown that both diverged from each other about 66-177 years ago, and with evolution, the AHFV strains became highly diversified. In 2007, from Jeddah, KSA, a strain of AHFV was found from an *O. Savignyi* tick viz., tick JE7.

When the sequencing of this strain was compared to that of the strain discovered in 1995, it was discovered that there is 99.7% nt sequence similarity in the envelope gene at its homologous region. Madani et al. in 2014, carried out a broad comparative analysis in which they compared the AHFV strain (from Najran) with 18 other AHFV strains (from Makkah and Jeddah), Dengue Virus (DENV), Langat Virus, KFDV, Tick-Borne Encephalitis Virus (TBEV), and Omsk Hemorrhagic Fever Virus (OHFV) [10,16,21,46]. In 2014, Madani et al. sequenced an AHFV strain isolated from Najran, having 10 546 nt long genome and encoding a single 5410 amino acid long polyprotein. The Narjan sequence of the AHFV strain was relatively short compared to previously isolated AHFV strains with 10 685 to 10 749 nt [47-49]. A comparative phylogenetic study of various strains of AHFV revealed that the Najran strain was very close. It shares about 99% homology with distinct 18 AHFV strains while other *Flaviviridae* family viruses like KFDV, OHFV, TBEV, and Langat virus isolates showed different clusters due to high variability in their sequence [48,49]. It was found that there is a variation in the sequence of the core protein and *NS4a* gene of the two different AHFV strains. The factor responsible for varying phylogenetic position and genome lengths of various strains from Najran and other region, was the recombination in virus strains [48,49].

PATHOGENESIS AND PATHOLOGY

AHFV was first identified as a KFDV variant in 1995 [50,51]. It was clear since it had 89% nt sequence homology [48,49,51]. The pathogenic mechanism of KFDV and AHFV involves the standard process seen in Flaviviruses, where the envelope protein (E) attaches to the cell surface with glycosaminoglycans. The virus then enters the cell through receptor-mediated, clathrin-dependent endocytosis. The endocytic vesicles with the virus then move to endosomes, where the acidic conditions cause the separation of the E protein's dimeric form into monomers, which then combine to form trimers. This change in

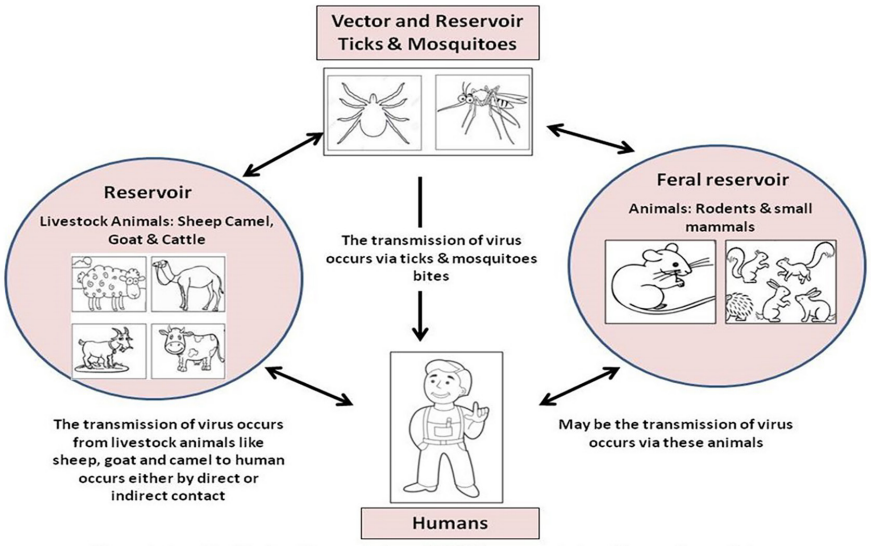

Figure 3. **Possible modes of transmission**.

shape results in the breaking apart of particles, merging of the viral and endocytic membrane, and the viral genome being released into the cytoplasm. The positive-stranded RNA is translated into one precursor polypeptide by ribosomes attached to the endoplasmic reticulum (ER), which is later separated into individual proteins by viral and host proteases. Genome replication takes place on host cell membranes derived from the ER, which are triggered by the virus to serve as a site for the viral replication complexes and host cell factors essential for replication. Ultimately, the viral RNA binds with the C protein and is enclosed within a lipid bilayer derived from the ER, which includes hetero-dimers of the prM and E proteins. The C protein helps virus budding by attaching to the ER membrane and containing the viral genome. The virions are then moved to the Golgi complex for the ultimate maturation phase, where prM is converted into M through furin-mediated cleavage. This procedure guarantees that the premature virus particle does not merge with the cell membrane while being exported. Mature infectious particles are discharged into the extracellular environment through exocytosis originating from the Golgi apparatus.

Dodd et al. (2014) conducted the initial animal-model study on the pathogenicity of AHFV. Even though both AHFV and KFDV were shown to infect various organs in mice, AHFV had lower lethality and viral levels compared to KFDV [52,53]. Histopathological analysis of AHFV-infected rat brains revealed the presence of meningoencephalitis, but with sporadic inflammatory infiltration and no necrosis detected. Additionally, the research demonstrated that the brain abnormalities in AHFV-infected rats were comparable to those detailed by Holbrook et al. (2005) [54] in their examination of the brains of Powassan virus-infected mice. Nevertheless, some regions of the cerebrum of mice infected with the Powassan virus showed necrosis in the form of acute neuronal injury, edema, and karyorrhexis. Conversely, OHFV-infected mice showed signs of patchy meningoencephalitis with perivascular cuffing and no necrosis in their brains [54]. In contrast, a previous experiment using a BALB/c mouse model showed that AHFV did not result in observable illness, being present in various internal organs and causing only slight histopathological changes, as well as triggering a proinflammatory response in the spleen and kidney [55]. In a recent study using mice without the type I interferon receptor, Bhatia et al. showed that AHFV-induced damage was primarily seen in the spleen, liver, heart, and lymph nodes with no observed changes in the lungs, kidney, or brain [17]. Because of sporadic and unforeseen occurrences of VHF resulting from specific viral infections like AHFV and KFDV a limited clinical and epidemiological information is available hence incomplete data on pathogenesis is available [56].

MODES OF TRANSMISSION

The mode of transmission of AHFV is influenced by several factors like age, sex/gender of patients, weather conditions, etc. Other important factors that affect the transmission are direct and indirect contact with the livestock and their products like meat, raw milk, blood, and body secretions, etc. Contamination can be due to improper housing conditions of livestock animals, especially camels and sheep, which have been exposed to ticks and mosquitoes that are later on responsible for infection (Figure 3). Most of the AHFV infections were reported from such areas with regular contact between livestock animals like localities nearby to the slaughterhouses and

butcher areas. It was evident from the study of by Qattan et al. where first eight cases of AHFV infection resulted due to contact with sheep; out of these eight patients, six were butchers [57]. It became clear that the transmission of AHFV infection is either due to direct contact of humans with livestock animals or their different products; there is also a possibility of transmission through mosquito bites, which indicated that ticks might either act as vectors or as reservoirs for transmission of AHFV [1,9,18,58-60].

It was also discovered that patients who had no interaction with infected animals or their products, as well as no tick bites, contracted the virus. It was later discovered that these individuals had been bitten by mosquitos, however this does not establish that mosquitos operate as vectors or reservoirs for AHFV. These people either lived or worked in areas near livestock animals or animal markets or near to slaughterhouses. These findings revealed that mosquitoes were most likely to be the vector of these viruses infecting animals first and later humans. Another study reported that the handling of raw milk or animal meat products was insignificant compared to direct contact with livestock animals, tick bites, and neighboring animal farms. The transmission of AHFV infection from one human to another remains unclear. Despite the fact that there have been multiple incidences of human-to-human transmission of AHFV infection within the same family.

The transfer of infection through the air-droplets, close contact with infected individuals, or transmission by their body fluids is yet to be studied. It is also evident that transmission of AHFV in a group may be due to predisposition to a common source of infection or vectors *viz* mosquitoes or ticks. It is still unclear that which is/are vectors of this AHFV infection; one of the important suspects is mosquito. Additionally, several reports show that AHFV was transmitted from animals and their products to an individual is either by direct contact or by ticks, this scenario becomes clear in agricultural areas from where diseases were reported. Under such circumstances, from 2007 to 2017 there were seven reports published that shows that the transmission of this virus occurred from ticks discovered AHFV RNA in the camel tick *O. savignyi* from Jeddah, KSA [16,22,45]. Following that, Mahdi et al. isolated AHFV from *H. dromedarii* and sand tampan ticks (*O. savignyi*) in Najran, KSA. Carletti et al. [12] reported that two Italian tourists returning from Egypt had clinical AHFV infection and that one of them had been bitten on the foot by an arthropod described as tick-shaped but not formally recognized. Ravanini et al. [14] and Musso et al. [13] both described AHFV cases involving Italian tourists returning from Egypt who were exposed to an unidentified tick-shaped bug. Horton et al. [50] discovered AHFV RNA in *Amblyomma lepidum* ticks from imported cattle in Djibouti. In April 2017, AHFV RNA was detected in three patients in Algunfuda, KSA, who had also been bitten by unidentified ticks (personal communication, Ministry of Health, Jeddah, Saudi Arabia). As a result of the above observations, ticks may play an essential role in the epidemiology of AHFV, perhaps as viral vectors or reservoirs. More study in this area is needed to understand the relationship between ticks, mosquitoes, and AHFV transmission due to lack of research.

CLINICAL MANIFESTATIONS

Clinically, AHFV infection varies from subclinical to severe or even fatal. Clinical symptoms include retro-orbital pain, fever, headache, leucopenia, vomiting, myalgia, thrombocytopenia, arthralgia, and anorexia. Severe infection can cause hemorrhagic symptoms such as hematemesis, epistaxis, and, in rare cases, encephalitis. Individuals suffering from encephalitis complications die, and such cases have a 25% mortality rate [1,10,14,41,62]. Laboratory manifestations or symptoms involve an increased level of lactate dehydrogenase, creatine kinase, and other liver enzymes. During outbreaks of AHFV in places like Jeddah, Makkah, Najran, and other areas in KSA there were numerous reports focusing on clinical and laboratory manifestation that was seen in these areas. Some examples includes fever, headache, malaise, arthralgia, anorexia, myalgia, backache, nausea and vomiting, chills, retro-orbital pain, diarrhea, abdominal pain, hemorrhagic manifestations, CNS manifestations, leucopenia, high level of liver enzymes, prolonged partial thromboplastin time, thrombocytopenia, increased level of creatine kinase level, and of lactate dehydrogenase. In addition to these common symptoms, a peculiar case of AHFV was noticed, in which the patient had "Rhabdomyolysis and severe muscle weakness" [1,3,10,14].

As for the question of its treatment, no antiviral drug/s have been invented yet. The treatment of AHFV includes symptomatic treatment, for example giving intravenous fluids and ionotropic supplements, in severe conditions. Other treatments can be adopted, like transfusion of fluids, like plasma and blood, giving oxygen by mechanical means, and in case of secondary infections antimicrobial mode of therapy is needed. There are several challenges in AHFV treatment. The first is to develop specific treatment and vaccines that will be available in the future to combat AHFV infections, and the second is to have an animal model for AHFV for testing and determining potent drug targets that will best and suitably control AHFV.

DIAGNOSTIC METHODS

Detecting early diagnosis of AHFV involves several molecular and immunological techniques [15,60]. Immune-fluorescence assay (IFA) was used to detect *Flavivirus* specific monoclonal antibodies 4G2. A Polymerase chain reaction (PCR) based 220-base pairs long gene having 89% homology with KFDV NS5 gene was used for the diagnosis of AHFV. Culturing viruses are usually time-consuming and more complicated as compared to Real-time PCR (RT-PCR) [23]. The suspected infection of AHFV can be detected by RT-PCR of body fluid for examples plasma and serum of patients. The initial 7 days of suspected infection is very crucial for its detection and sampling for these tests must be done in the first 7 days to give better detection results. Another point that to be mentioned here is that using buffy coats of individuals having suspected infection gives enhanced sensitivity and also good specificity as compared to using other body fluids, like blood and serum. Various other alternative diagnostics methods are in the pipeline to develop diagnostics assays like other infectious diseases [63-69] and for vaccinations to approach screening of vaccine candidates [70,71].

AHFV ANTIBODIES AND ITS SURVEILLANCE IN HUMAN SERUM

There are very limited sero-surveillance data available for human AHFV antibodies studies from KSA or elsewhere. These data on sero-surveillance from KSA showed the lack of AHFV IgM antibodies. Previously, it was assumed that AHFV-IgG of KSA is not prevalent and found in narrow dimensions, but sero-studies from different parts of KSA have unmasked this and showed that AHFV-IgG positive sera are present in 1.3% out of 1024 soldiers. It suggests broader geographic distribution [72]. To support such studies, it was found that local geographical distribution of AHFV-IgG positive sera has been reported in Tabouk (Northern region) 61.5%, Jazan (South Western region) 7.7%, and Eastern region 23.1% Asir (South Western region) 7.7%, respectively. A strange and intriguing phenomenon was reported in Djibouti, where no AHFV infection was identified, although there were AHFV-IgG positive people [73]. A sero-surveillance investigation in Djibouti found that among 893 people, only a 13-year-old girl who resided near an abattoir had AHFV-neutralizing antibodies [15,60,72]. The reality behind this may be either they have been exposed to AHFV or subclinical infection with AHFV.

PREVENTION AND CONTROL

The limited epidemiological data of AHFV suggests that the control and prevention of infection can be achieved by restricting direct contact with livestock animals and their products like raw milk, meat, etc., and avoiding tick and mosquito bites. The authorities like municipalities, sanitary, health, and veterinary departments near slaughterhouses, animal marketplaces, or infected places should be called immediately to evaluate the risk factors, take action, and propagate awareness among the population regarding its spread and its safe handling measures while treating an infected individual. There should be the establishment of a national-level prevention and control program in this regard. It is observed that countries having such well-equipped national-level prevention and control programs reported a drastic decrease in infection. Avoiding the infection is the only way to decrease the spread of AHFV infection along with interdisciplinary teamwork in the present scenario. Also, currently in progress is the development of human or animal vaccines to prevent this infection. An *in silico* analysis has recently been done for development of an epitope-based peptide vaccine against AHFV where the authors have analyzed the envelope glycoprotein of ALKV for developing B- and T-cells epitope-based peptide vaccine candidates [72,73]. Data from such studies suggest that these proposed epitopes can be used in the development of a vaccine for ALKV, which may induce both humoral and cell-mediated immunity.

MORTALITY DUE TO AHFV INFECTION

The epidemiological data of AHFV in KSA showed that the mortality rate in Jeddah and Makkah was 20% and 25%, respectively [3]. Subsequently, due to early diagnosis, awareness, improved healthcare, and sanitary facilities as well as the involvement of various authorities have been proven successful in decreasing mortality. For example, the mortality rate was 1% in Najran from 2003 to 2009. A very limited outbreak was observed in Taif and Jazan between 2010 and 2015, and it reached <0.5% in Algunfuda in 2017. Other various data have shown its range of illnesses from asymptomatic infections to severe and fatal infections. The decreasing death rate points out that the AHFV has reached endemicity which in turn leads to the development of herd immunity in the population.

SUMMARY

To summarize, AHFV is a novel hemorrhagic fever virus of *Flaviviridae* family that has mostly been reported in KSA. Because it originated in the Alkhumra neighborhood of Jeddah, it is known as the Alkhumra hemorrhagic fever virus (AHFV). Its clinical symptoms include flu-like disease, fever, hemorrhagic signs, and, in rare cases, encephalitis. The virus is transmitted from animals (such

as sheep, goats, and camels) to people by direct contact or through tick and mosquito bites, and they may operate as a vector or a reservoir. More research is needed to understand the involvement of AHFV vectors. The engagement of authorities such as towns, sanitary, health, and veterinary departments near slaughterhouses, animal marketplaces, or diseased areas to identify risk factors is one of the preventative methods. Different measures should be taken to raise public awareness about AHFV and its spread. People should be educated on how to safely handle diseased people, animals, or their products. There is an urgent need for extensive study on the role of arthropods (mosquitoes and ticks) as vectors, the role of animals in AHFV transmission in humans and cattle, and the seroprevalence of AHFV antibodies.

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