Review Article

Alkhumra Hemorrhagic Fever in Saudi Arabia

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ABSTRACT

Objective: Alkhumra virus (ALKV) was identified in 1994 as the agent of a hemorrhagic fever in Saudi Arabia. Genetic and phylogenetic analyses characterize it as a variant genotype of Kyasanur Forest disease virus (KFDV). Since then, several cases of Alkhumra hemorrhagic fever (ALKHF) with fatality rates as high as 25% have been documented in Saudi Arabia. The aim of the current article is to review and provide an insight into ALKHF in Saudi Arabia.

Methods: Articles published between 1994 and 2014 on ALKV and ALKHF were studied by reviewing the Medline/PubMed databases - the online Google Scholar database and the ProMED database using the keywords Alkhumra virus, Alkhumra Hemorrhagic fever, Kyasanur Forest disease virus, Viral hemorrhagic fever, Zoonotic disease.

Results: ALKV is a tick-borne flavivirus that causes hemorrhagic fever in humans. It is transmitted from animals to humans and has a seasonal pattern peaking during March to July. Subcutaneous and internal haemorrhages are common. The presence of neurological signs and altered liver function tests are associated with higher mortality rates.

Conclusion: ALKV is a hyper virulent tick-borne flavivirus that causes hemorrhagic fever in humans with high fatality rates. Better understanding of the disease can be facilitated by the application of universally agreed upon surveillance protocols in order to assist in increasing awareness, early identification and better management of those affected. In view of the lack of such protocols, the one formulated by the Saudi Arabian Ministry of Health in 2010 appears to be an appropriate protocol for widespread use.

KEY WORDS: Alkhumra virus
Alkhumra Hemorrhagic fever
Kyasanur Forest disease virus

Introduction

Alkhumra hemorrhagic fever (ALKHF) acquired its name from the town of Alkhumra near Taif, east of Jeddah, Saudi Arabia, where the first case was discovered in 1994-1995 [1,2]. After that, it was detected in Makkah in 2001-2003. The new hemorrhagic fever virus (Alkhumra virus), was misnamed as Alkhurma virus but was then recognized by the International Committee on Taxonomy of Viruses (ICTV) as Alkhumra virus [3-5]. Subsequently it was reported from Najran, in southern Saudi Arabia [1, 6-8]. Soldiers relocating to Jazan province from Tabuk, Asir and the Eastern Province in Saudi Arabia, showed serological evidence of the virus, suggesting that ALKHF is more widespread than previously thought [9]. In 2010 it was also reported in tourists returning to Italy from Egypt where ALKV had not been previously reported Figure 1 [10, 11].

General features

ALKHF is a zoonotic disease, the reservoir hosts are camels, goats and sheep. Involvement of other mammals is yet to be documented. Routes of transmission are:

1. Transcutaneously, through the bite of an infected tick or by skin wound contamination with raw uncooked meat or blood of an infected vertebrate and

2. Orally, through drinking of unboiled contaminated milk [6,8,10, 12,13]. Transmission to humans has been linked to butchering of camels and sheep (a major event in the holy Islamic ritual of Hajj) but no human-to-human transmission has been reported [10].

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In 2004 - 2005 ALKV RNA was detected in Jeddah both in the soft tick Ornithodoros savignyi, collected from camels and their resting places, as well as the hard camel tick Hyalomma dromedarii [1,8,12]. *Ornithodoros savignyi* the sand tampan (Karapatti), is a cryptic, nocturnally active, sand-dwelling soft tick that bites animals, mostly camels and sheep resting under trees as well as humans [8,14]. The route of tick-to-tick transmission is most likely the cofeeding of uninfected and infected ticks in close proximity on an infected vertebrate [15]. Tick remains infected throughout its life cycle and so acts as a vector and transmitter of ALKV Figure 2 [16].

Figure 1. Distribution map with added on red coloring to mark geographic areas where cases of ALKHF have been reported [11].

Figure 2. The external morphology of an Ornithodoros savignyi tick-sand tampan (Karapatti). The length of this animal was approximately 10 mm. Google images, ceded by Stephen Barker. Photo: Jaqueline Matias [16].

Dorsal view Ventral view

Challenges

Flaviviruses are typically transmitted by either mosquitoes or ticks, but in the recently confirmed human ALKHF cases no mosquitoes were incriminated [17]. Studies reporting transmission of ALKV by mosquito, remain unverified and needs virologic analysis of field-collected mosquitoes for confirmation [1, 7, 18, 19]. In January 2010, a working committee in Saudi Arabia was assembled by the Saudi Arabian Ministry of Health (SAMOH) consisting of local and international experts, with five focus groups. The aim of this committee was to develop a national protocol (surveillance system) for countering ALKHF [3].

Virus classification & details

ALKV is a member of the Flaviviridae family (class IV), genus Flavivirus. It has a single stranded RNA genome & is a subtype of the Kyasanur Forest disease virus (KFDV) with 89% nucleotide sequence homology [20]. The virus genome uses host cell machinery to replicate [1,8, 20, 21]. Till to date, three tick-borne flaviviruses causing hemorrhagic fever in humans are documented. They are ALKV in western provinces of Saudi Arabia, KFDV in the southern Indian state of Karnataka and Omsk hemorrhagic fever virus in Siberia [22, 23]. Center for Disease Control and Prevention, USA has labeled these three viruses as hyper virulent pathogens and recommends biosafety level (BSL) 3-4 handling facilities (the level of biological containment used for infectious agents that cause fatal infections for which there is no treatment or vaccine) because of their potential to be used in biological warfare [13]. Saudi Arabia categorizes ALKV as a BSL 3 agent [18].

Epidemiological data

Epidemiological data are scarce due to the lack of a uniform ALKV surveillance system [7,8,10,13,20]. During 1994 - 1999, eleven clinical cases were found in Makkah province in a seasonal pattern from March - July. This finding supports disease association with peak tick activity beginning in March [1,12,14]. From February 2001 to January 2003, a total of 37 cases were identified in Makkah province. Although 11 of them had hemorrhagic manifestations and 5 died, only 20 were lab-confirmed. Analysis of the seasonal distribution of cases showed that they occurred in two peaks rather than one, the first from March to June and the second from September to October [1,7]. From August 2003 to December 2009, out of 148 cases reported in a descriptive cohort study from Najran, 78 (52.7%) cases were serologically confirmed [1]. On January 2010, the SAMOH announced that a total of 7 cases of ALKV infection had been detected in Makkah and Najran. Four were linked to Hajj 2009, with the victims having been involved in slaughtering or processing sheep [23]. In another descriptive study, 174 laboratory confirmed cases of ALKHF were reported in 2010 & 2011 with lesser incidence of hemorrhagic & neurologic manifestations & a very low fatality rate of 0.43% [24]. Hepatic involvement was not noted and hematological & biochemical data were not provided in this study. In 2010 two tourists returning to Italy after visiting the town of Shalatin in southeastern Egypt near the border with Sudan , which has a large camel market, were reported to have been infected with ALKV indicating that the disease is present in that part of Egypt [10].

Clinical features

Clinical features are similar to those of other tick-borne flaviviruses, especially Kyasanur Forest disease (KFD). The incubation period of ALKHF is unknown but is probably similar to other tick borne flavivirus infections (i.e., 3-8 days). The incidence of main clinical features and laboratory findings reported in two Studies are shown in (table 1) [1,7]. The physical findings are not well documented in the

noted studies except for the mention of facial erythema, lymphadenopathy and hepatosplenomegaly. The pathologic findings including gross and microscopic examination of tissues from fatal ALKHF cases have not been documented yet [1,7]. The criteria outlined by the SAMOH working committee for the identification of AHFV are shown in table 2.

Management

Preventive measures should include:

1. Avoiding tick-infested animals or animal habitat and markets.
2. Checking livestock periodically and using appropriate insecticides to ensure that they are free of ticks [25].
3. For those exposed to ticks or those in endemic areas:

Wearing gloves when handling raw meat and animal products [24]. Wearing pale-colored clothing for easy identification of ticks [26]. Using repellents and protective clothing impregnated with permethrin and by tucking trousers into socks [3, 26].

Regular self inspection and removal of any attached ticks carefully, while avoiding crushing or handling them with unprotected fingers [26].

While vaccines are available for tick-borne encephalitis (TBE) & Kyasanur Forest disease (KFD) [27], the prospect of developing a vaccine for ALKHF has yet to be explored.

Treatment:

Since the role of antiviral compounds in human infection with ALKV still needs to be established, treatment remains supportive.

Limitations of the study

The author acknowledges that there are limitations to this review, these include the availability of only a limited number of original articles on the topic with scarcity of clinical data & public health risk assessment in the few articles available. In addition, there is an absence of studies to characterize the distribution of ALKV in the Arabian Peninsula as well as an absence of an internationally applied surveillance protocol.

Discussion

ALKHF is a tick-borne zoonotic hemorrhagic infection discovered and notifiable in Saudi Arabia. Its prevalence in humans in the affected areas of Saudi Arabia is unknown, and its recent detection in tourists visiting southern Egypt suggests that the geographic distribution of this virus could be wider, and the numbers of those affected much higher than previously thought.

Table 1. Incidence of Clinical features and laboratory findings in laboratory-confirmed Alkhumra virus infection in Saudi Arabia from 2001 to 2009 reported from 2 studies.

Clinical features	Study 1* (37cases-20 lab confirmed) Percentage of patients	Study 2* (148cases-78 lab confirmed) Percentage of patients	Mean
General			
Fever	100	100	100
Chills	25	60.3	42.65
Malaise	75	85.9	80.45
Myalgia	75	82.1	78.55
Arthralgia	45	83.3	64.15
Retro-orbital pain	5	55.1	30.05
Backache	25	71.8	48.40
Hemorrhagic manifestations	55	25.6	40.30
Epistaxis	25	11.5	18.25
Petechiae/Purpura	20 / 5	0 / 1.3	20 / 3.15
Hematemesis/Melena	20 / 5	6.4 / 2.6	13.2 / 3.8
Gastrointestinal bleeding	20	7.7	13.85
DIVC/ Shock	15 / 10	3.8 / -	9.4 / 10
Neurologic manifestations	35	23.1	29.05
Headache	75	85.9	80.45
Confusion	25	10.7	17.85
Drowsiness	25	21.8	23.40
Neck stiffness	-	9.3	9.30
Encephalitis	20	12.8	16.40
Convulsion	5	5.1	5.05
Coma	20	5.1	12.55
Hepatic involment			
Jaundice	5	1.3	3.15
Hepatitis	100	5.1	52.55
GIT manifestations			
Anorexia	20	82.1	51.05
Nausea/vomiting	50	71.8	60.90
Abdominal pain	10	48.7	29.35
Diarrhoea	20	51.3	35.65
Rash	15	0	7.5
Lab. Variable			
Hemoglobin <110 g/L	5	8.1	6.55
Leukopenia <3.0 x 10^9/L	65	87.7	76.35
Platelets < 100 x10^9/L	75	46.2	60.60
INR > 1.2	45	23.8	34.40
PTT > 45 s	75	52.6	63.80
Bilirubin >17 mmol/L	30	12.8	21.40
AST > 40 U/L	100	85.7	92.85
ALT > 40 U/L	80	67.2	73.60
CK > 400 U/L	95	45.7	70.35
LDH > 500 U/L	85	25	55.00
Case Fatality	25	1.3	13.15

*Study 1 & 2 by courtesy of Madani TA [1, 7]

Table 2 The identification criteria for clinical cases set by the SAMOH working Committee [3].

Clinical case definition
1. Suspected: Case meets the clinical and exposure criteria.
2. Probable: suspected case with clinical laboratory data (e.g., thrombocytopenia, leucopenia, elevation of liver enzymes, elevated CPK or LDH) and IgM detected by capture ELISA.
3. Confirmed: Probable case and laboratory criteria listed below.
Clinical criteria
Unexplained acute febrile illness (fever 38°C) with one of the three following features:
1. Hemorrhagic manifestations not related to injury (bleeding under the skin, in internal organs or from body orifices; and positive tourniquet test).
2. Liver involvement (jaundice, hepatomegaly).
3. Neurological involvement (severe headache, altered mental status, and/or seizures).
Laboratory criteria
One or more of the following laboratory findings:
1. AHFV RNA detected by real-time or conventional RT-PCR.
2. Virus isolation/identification using cell culture or suckling mice.
3. Four-fold antibody (IgG) rise in paired serum samples using ELISA or IFA.
4. Neutralization test-preferably plaque reduction for paired sera.
Exposure criteria
One or more of the following exposures before onset of symptoms:
1. Recent contact with animal, blood or other animal products.
2. Recent exposure to or bite by tick.
3. Contact with blood or body fluid from a confirmed human case.
4. Work in a laboratory that handles AHFV specimens/isolates.

While related flaviviruses can be transmitted through the milk of infected livestock, which has been noted as a risk factor in ALKV infection by some [28,29], the role of arthropods such as mosquitoes, rodents and other mammals in the transmission and maintenance of the virus needs to be confirmed.

Potential vectors (mosquitoes, midges, sand flies, etc.) should be tested for AHFV and evaluated for vector competency, and the possible role of bats and birds in AHFV ecology should be evaluated, serologically and experimentally [3].

Other issues which need to be resolved are the origin of the virus, how it is dispersed, and how it came to Saudi Arabia, so that proper disease control strategies may be devised. A better understanding of the disease can be facilitated by the application of universally agreed upon surveillance protocols. In view of the lack of such protocols, the one formulated by the SAMOH in 2010 appears to be an appropriate protocol for widespread use [3].

In spite of the limitations faced by this study, this review provides both a comprehensive summary of what has been published previously as well as a platform for further studies on this important life-threatening infection.

Recommendations:

Multinational epidemiological and serological studies are needed to determine the regional distribution (of both asymptomatic and symptomatic cases), natural history and pathogenicity of this viral infection in the Arabian Peninsula and elsewhere, by the application of SAMOH surveillance protocol.

The virus should be included in the list of travel-related pathogens under surveillance and Hajj pilgrim & travellers should be advised about the risks of coming in contact with animals in endemic areas. The Ministries of Health and Agriculture should collaborate in launching an educational program for abattoir workers in the endemic areas of Saudi Arabia. Also Clinicians should be aware of risks and strategies (SAMOH surveillance protocol) to manage them, since there are no therapeutic options for combating this disease. Caution should be exercised when blood donation involves persons at risk in endemic area, as it is not known whether transfusion-mediated transmission of ALKV is possible due to lack of screening protocol. KFD vaccine in India & TBE vaccine in Russia and Europe are highly effective. In absence of immunoprophylactic measures available against ALKHF, opportunities to adapt these vaccines to local AHFV infection prevention program should be explored due to the antigenic cross-reactivity between these viruses.

Conflict of Interest

I declare that we have no conflict of interest.

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