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一般的名称	①ポリエチレングリコール処理抗破傷風人免疫グロブリン ②乾燥抗破傷風人免疫グロブリン		研究報告の 公表状況	Journal of Infection 51(2) 91-97, 2005	公表国 サウジアラビア	
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研究報告の概要	サウジアラビア Alkhumra 地区で 1995 年に 6 人の Dengue 出血熱のような患者からダニ媒介性のキャサナル森林熱ウイルスに非常に類似した新種のフラビウイルスが発見され、ALKV (Alkhumra virus) と命名された。サウジアラビア Makkah で 2001 年 2 月 8 日～2003 年 2 月 9 日の間に ALKV 感染の疑いのある患者 37 例が確認され、その内 20 症例から ALKV が検出された。急性発熱性のインフルエンザ様疾患患者の主臨床像は肝炎 (100%)、出血兆候 (55%) 及び脳炎 (20%) であった。致死率は 25% であった。疾患はヒツジヤヤギとの直接接触又は蚊刺傷からヒトに伝播する新しい人畜共通出血熱ウイルスと考えられる。蚊やダニのような節足動物、ヒツジ、ヤギ、げっ歯類のような動物でのウイルス伝播や保持の役割について解明する必要がある。					使用上の注意記載状況・ その他参考事項等
	報告企業の意見					今後の対応
サウジアラビアで起きたキャサナル森林熱ウイルスに非常に類似したフラビウイルス ALKV (Alkhumra virus) による感染症が、重篤な出血性の人畜共通感染症であることが判明したとする報告である。万一、原料血漿に ALKV が混入したとしても、BVD をモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。					本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	





Alkhumra virus infection, a new viral hemorrhagic fever in Saudi Arabia

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Abstract Objectives. Four patients with typical acute viral hemorrhagic fever were identified in the holy city of Makkah, Saudi Arabia, between 8 and 23 February 2001, the Hajj (pilgrimage) period of that year. Tests for Rift Valley fever (RVF), Crimean-Congo hemorrhagic fever (CCHF), and dengue were negative. Blood specimens were sent to the Centres for Disease Control and Prevention (CDC), Atlanta for viral culture and testing for other hemorrhagic fever viruses. A new flavivirus closely related to the tick-borne Kysanur forest disease virus was isolated. This new flavivirus was originally isolated in 1995 from 6 patients with dengue-like hemorrhagic fever from Alkhumra district, south of Jeddah, Saudi Arabia.

Methods. A case definition was formulated for surveillance of this new disease in Saudi Arabia. Blood specimens were collected from all patients with suspect 'Alkhumra' virus (ALKV) infection and tested for ALKV, RVF, CCHF, dengue, and West Nile encephalitis. Patients data were prospectively collected on standardized data collection forms.

Results. From 8 February 2001 through 9 February 2003, a total of 37 cases were identified in Makkah, 20 of them were laboratory confirmed. Acute febrile flu-like illness with hepatitis (100%), hemorrhagic manifestations (55%), and encephalitis (20%) were the main clinical features. The case fatality was 25%. The disease seemed to be transmitted from sheep or goat to humans by the mosquito bites or direct contact with these animals.

Conclusions. ALKV infection is a novel serious zoonotic hemorrhagic fever virus discovered in Saudi Arabia. The role of arthropods such as ticks and mosquitoes, and animals such as sheep, goat, and rodents in the transmission and maintenance of the virus remains to be elucidated.

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Introduction

After the appearance of Rift Valley fever (RVF) in Saudi Arabia for the first time outside the African continent in September 2000, the Saudi Ministry of

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Results

From 8 February 2001 to 9 February 2003, a total of 37 cases fulfilled the case definition of ALKV infection, 20 cases of which were laboratory confirmed. Tests for RVF (antigen, IgM, IgG, RT-PCR, culture), CCHF (IgM, IgG, antigen), Dengue (IgM, IgG, RT-PCR), and West Nile encephalitis (IgM, antigen, RT-PCR) were negative in the 37 patients. All 37 suspect cases were reported from Makkah. All cases either lived or visited districts in Makkah that had livestock marketplaces or slaughterhouses (Al-Sharaye, Al-Kakia, Al-Shemaisi, Al-Moaysem). Table 1 summarizes the demographic characteristics and possible risk factors for acquiring the disease in the laboratory-confirmed cases. The mean (\pm standard deviation) age of patients was 33.4 (\pm 13.6). No cases were reported among children less than 10 years of age. The disease predominantly affected male patients with a male to female ratio of 9:1. None of the patients who had contact with animals reported animal abortion, disease, or death.

Table 2 shows the clinical features and complications in 20 patients with laboratory-confirmed ALKV infection. Eleven (55%) patients had one or more of the following hemorrhagic manifestations: epistaxis (5 patients, 25%), ecchymoses (4 patients, 20%), petechiae (4 patients, 20%), hematemesis (4 patients, 20%), bleeding from gum (3 patients, 15%), bleeding from puncture sites (3 patients, 15%), melena (1 patient, 5%), and purpura (1 patient, 5%). Seven (35%) patients had one or more of the following central nervous system manifestations: confusion (5 patients, 25%), drowsiness (5 patients, 25%), coma (4 patients, 20%), convulsion (1 patient, 5%), and irritability (1 patient, 5%).

Table 3 shows the laboratory characteristics on admission, and Table 4, the mean values and range of laboratory results on admission, for 20 patients hospitalized with laboratory-confirmed ALKV infection. Table 5 presents the confirmatory laboratory test results and the time period in days between the onset of illness and the collection of blood specimens for testing for each patient with laboratory-confirmed ALKV infection. None of the patients had the virus isolated from Vero E6 cells alone nor did any patient have a positive RT-PCR alone. None of the patients with positive IgG or IgM antibodies had a positive culture or RT-PCR. The mean duration between the onset of illness and the collection of blood specimens from patients who were positive for only IgM was 5 days, and from patients who were positive for only IgG was 10 days. For patients who

Table 1 Demographic characteristics and risk factors for 20 patients with laboratory-confirmed Alkhumra virus infection in Saudi Arabia

Variable	Number of patients (%)
Age, mean \pm SD, range (year)	33.4 \pm 13.6, 11- 60
Age groups (year)	
<10	0
10- <20	3 (15)
20- <30	5 (25)
30- <40	6 (30)
40- <50	3 (15)
50- <60	2 (10)
\geq 60	1 (5)
Gender	
Male	18 (90)
Female	2 (10)
Nationality	
Saudi Arabia	8 (40)
Bangladesh	5 (25)
Other nationalities ^a	7 (35)
Occupation	
Laborer	10 (50)
Office employee	3 (15)
Student	3 (15)
Butcher	1 (5)
Driver	1 (5)
Housewife	1 (5)
Soldier	1 (5)
Risk factors	
Living in or visiting districts that have livestock marketplaces or slaughterhouses in Makkah ^b	20 (100)
Mosquito bites only	9 (45)
Direct contact with sheep or goat only	3 (15)
Mosquito bites and direct contact with sheep or goat	5 (25)
Tick bites	0
Drinking raw milk	0
Contact with a patient with a similar illness	1 (5)
Number of patients reporting abortion storms, disease, or extraordinary deaths among animals	0

^a Egypt, 2 patients; Yemen, 2 patients; Burma, 1 patient; Ethiopia, 1 patient; Pakistan, 1 patient.

^b Al-Sharaye, Al-Kakia, Al-Shemaisi, Al-Moaysem.

were positive for only IgG, convalescent sera to test for a rising IgG titre were not obtained because patients were either deceased or discharged from the hospital and not available for testing. However, these cases were considered to have confirmed ALKV infection because of their typical clinical

Table 5 Confirmatory laboratory results for 20 patients hospitalized with laboratory-confirmed Alkhumra virus infection in Saudi Arabia

Test(s)	Number of patients (%)	Days between onset of illness and collection of blood for each patient
IgM only	3 (15)	3, 5, 7
IgG only	8 (40)	7, 8, 8, 9, 10, 10, 13, 17
IgM and IgG	4 (20)	5, 7, 8, 17
Isolation from suckling mice only	3 (15)	5, 6, 7
Isolation of the virus from Vero E6 cells and from suckling mice	1 (5)	3
Isolation of the virus from Vero E6 cells and from suckling mice, and a positive RT-PCR	1 (5)	3

fever) viruses; Bunyaviridae, which include RVF, CCHF, and the hantaviruses causing hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome; Filoviridae, which include Marburg and Ebola viruses; and Flaviviridae, which include yellow fever, dengue, tick-borne encephalitis, Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhumra viruses. Most hemorrhagic fever viruses are zoonotic, with the possible exception of the four dengue viruses, which may continually circulate among humans.⁶ Many VHF viruses are vector-borne (RVF, CCHF, yellow fever, dengue, tick-borne encephalitis, Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhumra viruses), while others are not (Lassa, Junin, Machupo, Guanarito, Sabia, Hantaviruses, Marburg, and Ebola viruses).

ALKV is the fourth VHF identified in Saudi Arabia; the other three are CCHF, dengue fever, and RVF. CCHF caused an outbreak in Makkah in 1990, after which the disease has not been reported in Saudi Arabia.⁷ Dengue fever caused an outbreak in Jeddah, Western Province, in 1994. Few more

cases have since been sporadically reported from Jeddah.⁸ Three of the four VHF diseases identified in Saudi Arabia, namely ALKV, CCHF, and Dengue, are thus confined to Makkah and Jeddah which are 80 km apart in the Western Province. The occurrence of ALKV and CCHF in these two cities is likely related to the importation of large numbers of livestock into Makkah city through the seaport, Jeddah, for the Hajj season. On the other hand, RVF the fourth VHF identified in Saudi Arabia, caused a major epidemic in 2000-2001 in three different areas in the southwest of Saudi Arabia, namely Jizan, Asir, and Alqunfuda, that are far from Makkah city.⁹

The epidemiological, clinical, and laboratory characteristics of ALKV are similar to RVF infection.⁹ Both diseases seem to be transmitted to humans by the mosquito bites and/or direct contact with infected sheep and goat. No confirmed cases of either ALKV or RVF infection were reported in children less than 10 years of age. Men were predominantly affected in the two diseases largely because of animal-related occupation. Unlike RVF,

Table 6 Mortality in those with, vs. those without, selected complications in 20 patients with laboratory-confirmed Alkhumra virus infection in Saudi Arabia

Complication	Patients with the complication			Patients without the complication			P
	Total	Died	%	Total	Died	%	
Bleeding manifestations	11	4	36.4	9	1	11.1	0.32
CNS manifestations	7	5	71.4	13	0	0	< 0.01
Creatinine > 150 µmol/l	5	3	60	15	2	13.3	0.07
AsT > 200 U/l	13	5	38.5	7	0	0	0.11
ALT > 200 U/l	9	4	44.4	11	1	9.1	0.13
Platelets < 100 × 10 ⁹ /l	15	5	33.3	5	0	0	0.27
LDH > 500 U/l	17	5	29.4	3	0	0	0.54
CK > 400 U/l	19	5	26.3	1	0	0	1.0
Leukocytes < 3 × 10 ⁹ /l	13	2	15.4	7	3	42.9	0.29
Bilirubin > 17 µmol/l	6	4	66.7	14	1	7.1	0.01

Abbreviations: ALT, alanine transferase; AsT, aspartate transferase; CNS, central nervous system; CK, creatine phosphokinase; LDH, lactate dehydrogenase.

- and IgM antibody findings among EHF patients in Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis* 1999; 179:5177-587.
4. Logan TM, Linthicum KJ, Moulton JR, Ksiazek TG. Antigen-capture enzyme-linked immunosorbent assay for detection and quantification of Crimean-Congo hemorrhagic fever virus in the tick, *Hyalomma truncatum*. *J Virol Methods* 1993;42:33-44.
 5. Shoemaker T, Boulianne C, Vincent MJ, et al. Genetic analysis of viruses associated with emergence of Rift Valley fever in Saudi Arabia and Yemen, 2000-01. *Emerg Infect Dis* 2002;8:1415-20.
 6. LeDuc JW. Epidemiology of hemorrhagic fever viruses. *Rev Infect Dis* 1989;11(Suppl 4):S730-S5.
 7. El-Azazy OME, Scrimgeour EM. Crimean-Congo haemorrhagic fever virus infection in the Western Province in Saudi Arabia. *Trans R Soc Trop Med Hyg* 1997;91:275-8.
 8. Fakeeh M, Zaki AM. Virologic and serologic surveillance for dengue fever in Jeddah, Saudi Arabia, 1994-1999. *Am J Trop Med Hyg* 2001;65:764-7.
 9. Madani TA, Al-Mazrou YY, Al-Jeffri MH, et al. Rift Valley fever epidemic in Saudi Arabia; epidemiological, clinical, and laboratory characteristics. *Clin Infect Dis* 2003;37:1084-92.
 10. Work TH, Trapido H. Kyasanur forest disease, a new virus disease in India. *Indian J Med Sci* 1957;11:341-5.
 11. Monath TP, Heinz FX. Flaviviruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE, editors. *Fields virology*. Philadelphia, PA: Lippincott; 1996. p. 961-1034.