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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<br>②乾燥抗破傷風人免疫グロブリン  | 研究報告の<br>公表状況                        | Journal of Infection<br>51(2) 91-97, 2005 | 公表国<br>サウジアラビア   |          |
| 販売名<br>(企業名)  | ①テタノプリン-IH (ベネシス)<br>②テタノプリン (ベネシス)  |                                      |   |                  |          |
| 研究報告の概要   | <p>サウジアラビア Alkhumra 地区で 1995 年に 6 人のデング出血熱のような患者からダニ媒介性のキャサヌ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。疾患はヒツジや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。</p> |                                      |   |                  |          |
| 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ヌ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、重篤な出血性の人獣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。 |   |                  |          |
| <p>使用上の注意記載状況・<br/>その他参考事項等</p> <p>代表としてテタノプリン-IH の記載を示す。</p> <p>2. 重要な基本的注意</p> <p>(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性で、かつ ALT(GPT) 値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査 (NAT) を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の破傷風抗毒素を含有する血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60°C、10 時間の液状加熱処理及び濾過膜処理 (ナノフィルターレーション) を施しているが、投与に際しては、次の点に十分注意すること。</p> |  |                                      |   |                  |          |



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

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## KEYWORDS

Alkhumra;  
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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 Kyasanur 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

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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

## 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 <sup>a</sup>   | 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 <sup>b</sup> | 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                       |

<sup>a</sup> Egypt, 2 patients; Yemen, 2 patients; Burma, 1 patient; Ethiopia, 1 patient; Pakistan, 1 patient.

<sup>b</sup> 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.<sup>6</sup> 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.<sup>7</sup> Dengue fever caused an outbreak in Jeddah, Western Province, in 1994. Few more

cases have since been sporadically reported from Jeddah.<sup>8</sup> 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.<sup>9</sup>

The epidemiological, clinical, and laboratory characteristics of ALKV are similar to RVF infection.<sup>9</sup> 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 <sup>9</sup> /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 <sup>9</sup> /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, créatiné phosphokinase; LDH, lactate dehydrogenase.

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