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MAJOR ARTICLE

Severe Human Illness Caused by Rift Valley Fever Virus in Mauritania, 2015

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Background. Rift Valley Fever epizootics are characterized by numerous abortions and mortality among young animals. In humans, the illness is usually characterized by a mild self-limited febrile illness, which could progress to more serious complications.

Objectives. The aim of the present prospective study was to describe severe clinical signs and symptoms of Rift Valley Fever in southern Mauritania.

Patients and methods. Suspected cases were enrolled in Kiffa (Assaba) and Aleg (Brakna) Hospital Centers from September 1 to November 7, 2015, based on the presence of fever, hemorrhagic or meningoencephalitic syndromes, and probable contact with sick animals. Suspected cases were confirmed by enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase-polymerase chain reaction (RT-PCR).

Results. There were thirty-one confirmed cases. The sex ratio M/F and the average age were 2.9 and 25 years old [range, 4-70 years old], respectively. Mosquito bites, direct contact with aborted or dead animals, and frequent ingestion of milk from these animals were risk factors observed in all patients. Hemorrhagic and neurological manifestations were observed in 81% and 13% of cases, respectively. The results of laboratory analysis showed high levels of transaminases, creatinine, and urea associated with thrombocytopenia, anemia, and leukopenia. All patients who died (42%) had a hemorrhagic syndrome and 3 of them had a neurological complication. Among the cured patients, none had neurologic sequelae.

Conclusion. The hemorrhagic form was the most common clinical manifestation of RVF found in southern Mauritania and was responsible for a high mortality rate. Our results justify the implementation of a continuous epidemiological surveillance.

Keywords. Assaba; Brakna; Mauritania; Rift valley fever; severe human illness.

Rift Valley fever (RVF) is a vector-borne viral disease caused by RVF virus (RVFV), a member of the *Bunyaviridae* family and *Phlebovirus* genus that primarily affects domestic ruminants, causing large epizootics with high mortality rates in young animals and abortions in affected female animals [1–5]. The virus was discovered in 1930 during an outbreak that affected livestock in East Africa [3–6], and 6 years later RVFV antibodies were found in human sera from southern Sudan [7]. The first major human epidemic occurred in 1951 in South Africa [6]. Since then, multiple outbreaks have been reported in different parts of Africa and the Middle East, notably in Egypt (1977, 2003) [8, 9], Kenya (1997–1998, 2006–2007) [10, 11], Tanzania (2007) [12], Somalia (2007), Saudi Arabia and Yemen (2000–2001) [4, 13], Sudan (2007, 2010) [7, 13], Mayotte (2008) [8], and Mauritania (1987, 1993–1994, 1998, 2003, 2010, 2012) [3, 9–13].

The disease occurrences follow the unusual trend of heavy rainfall leading to flooding, which provides a conducive environment for dormant mosquito eggs infected by RVFV to hatch and become predominant mosquito populations that transmit virus to animals and subsequently from animals to humans [1]. However, currently there is no evidence for person-to-person transmission of RVFV [1, 14, 15]. In humans, RVFV infection is typically asymptomatic or causes influenza-like illness accompanied by fever and headache but occasionally leads to serious complications, such as hemorrhagic syndromes, retinitis, encephalitis, and death [1, 4, 5, 16–18]. We report the results of a prospective study designed to determine the clinical pattern of RVF, the frequency of its complications, and the associated case-fatality rates among patients in Mauritania.

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PATIENTS AND METHODS

All suspected cases of RVF admitted at Aleg and Kiffa hospital centers from September 1, 2015 to November 7, 2015 were reviewed. Patients admitted at these hospitals mostly reside in Assaba, Brakna, Tagant, and neighboring regions. A suspected human case was defined as a person with febrile syndrome, either hemorrhagic syndrome (epistaxis, hemoptysis, melena, hematemesis, gingival bleeding, bruising) or meningoencephalitis, and probable contact with animals infected with RVFV. A confirmed case of RVF was defined on the basis of a positive laboratory test result. Blood sampling was undertaken for all suspected cases for detection of the viral genome by reverse transcription-polymerase chain reaction (RT-PCR) and/or serological enzyme-linked immunosorbent assay that detects specific anti-RVFV immunoglobulin (Ig)M antibodies. Plates were coated overnight at 4°C with IgM anti-μ-chain. The serum was then added, followed by RVF viral antigen. The detection antibody used is a high-titer anti-RVFV mouse ascitic fluid. Specific reaction was detected after addition of a horseradish peroxidase-conjugated anti-mouse IgG and revelation with the 3,3',5,5'-tetramethylbenzidine substrate. Sera were considered positive for antibodies if the difference between the sample and control optical densities was more than 3 standard deviations above the mean of the negative controls [19]. Viral ribonucleic acid (RNA) was extracted from 100 μL of serum by using the QIAamp RNA kit (QIAGEN, Inc., Chatsworth, CA) according to the manufacturer's instructions. Ribonucleic acid adsorbed on silica membrane was eluted in 50 μL of RNase-free water. Reverse transcription-PCR was done by using the Titan One-Step RT-PCR System (Roche Diagnostics, Mannheim, Germany) according to the recommendations of the manufacturer. Three previously described sets of primers, NS3a-NS2g, MRV1a-MRV2g, and Wag-Xg, were used to amplify fragments of the NSs, G2, and L coding regions, respectively [20–22]. The NSs coding region is located in the S segment, whereas the region coding for G2 and L are in the M and L segments, respectively. Laboratory analyses were performed at the National Institute of Public Health Research in Nouakchott (Mauritania) in collaboration with the Pasteur Institute of Dakar (Senegal).

A recently infected case was defined as a person with a positive RT-PCR or IgM-RVFV test. According to the World Health Organization, the severe form is defined as confirmed RVF associated with 1 or more of the following 3 syndromes: ocular (decrease in visual acuity), hemorrhagic, and/or meningoencephalitic syndromes. Malaria and hepatitis B (hepatitis B surface antigen) were screened for all suspected cases admitted at the hospitals. Differential diagnoses including salmonellosis, leptospirosis, and herpes infection were excluded. The examination of the optic fundus and brain imaging were not performed. Symptomatic treatment was initiated depending on the patient's needs (including blood transfusion, vasoactive amines, nasogastric feeding, analgesic-antipyretic).

RESULTS

From September 1, 2015 to November 7, 2015, 31 patients were found to be infected by RVFV. There were 31 confirmed cases among 57 patients screened: 23 were males (74%) and 8 were females (26%). The mean age was 25 years old (range, 4–70 years old). During the outbreak, 19 (61%) and 12 (39%) confirmed cases were admitted at Kiffa Hospital Center and Aleg Hospital Center, respectively.

The patients' occupations were as follows: 8 (26%) shepherds, 7 (23%) animal breeders, 1 (3%) farmer, 1 (3%) veterinarian, 1 (3%) baker, and 1 (3%) fisherman. All patients reported frequent mosquito bites, a direct regular contact with aborted or dead animals, and consumed milk provided by those animals. All patients declared not to have traveled out of the country during the 2 months before hospital admission. The mean duration from the onset of symptoms to hospitalization was 3 days (range, 0–8 days).

Overall, fever and hemorrhagic syndromes predominated. Dengue-like syndrome was observed in 6 patients (19%) on admission to hospital, and severe clinical manifestation, such as bleeding, was noted in 25 patients (81%). The proportions of other symptoms such as pallor, jaundice, and hepatomegaly were 94% (29 of 31), 84% (26 of 31), and 65% (20 of 31), respectively. The main clinical signs on admission are summarized in Table 1. Four patients (13%) had a combination of 2 serious

Table 1. Clinical Characteristics of 31 Cases of Severe Rift Valley Fever

Signs and symptoms	Frequency	Percent
Signs		
Pallor	29	94%
Jaundice	26	84%
Hepatomegaly	20	65%
Epistaxis	16	52%
Hematemesis	13	42%
Gingival bleeding	8	26%
Rectal bleeding and melena	8	26%
Splenomegaly	5	16%
Bloody mucoid diarrhea	2	6%
Vaginal bleeding	1	3%
Petechial rashes and ecchymoses	1	3%
Hemoptysis	1	3%
Symptoms		
Headache	12	39%
Nausea or Vomiting	12	39%
Anorexia	11	35%
Arthralgia and myalgia	10	32%
Abdominal pain	5	16%
Coma	4	13%
Dyspnea	3	10%
Hiccup	2	6%
Odynophagia	1	3%

manifestations, including hemorrhagic and meningoencephalitic syndromes. The most prominent abnormal laboratory findings found in all patients were marked elevations of serum levels of alanine aminotransferase, aspartate aminotransferase, creatinine, and urea. Thrombocytopenia, anemia, and leukopenia occurred frequently. Four patients (13%) had chronic hepatitis B (Table 2). Among all confirmed cases, 13 (42%) had hemorrhagic fever, 3 (10%) of whom had neurologic symptoms associated with the disease and died within 3 days (range, 0–7 days) of illness onset.

DISCUSSION

Regular outbreaks of RVFV have occurred throughout Africa for many years [2, 14], and the geographical range of RVFV is expanding due to climate change and human activity [14]. The occurrence of outbreaks of RVF is often associated with heavy rains and hydrographic changes, which result in the proliferation of mosquito vectors of RVFV [2, 15]. However, the mechanisms that enable the virus to persist at a low level between outbreaks remain poorly understood [15].

In Mauritania, the first human cases of RVF were reported in 1987 at Rosso during an outbreak that caused the deaths of 220 humans [23]. As a consequence of this outbreak, a surveillance system was developed to detect animal cases in Mauritania, Senegal, and other West African countries [24]. As in previous epidemics of RVF [3, 9–13], an outbreak of abortions and perinatal mortality in herds (sheep, goats, cattle, and camels) preceded the human epidemic in 2015. Entomological and virological investigations carried out in 2012 in Trarza, Tagant, Brakna, Assaba, and Hodh El Gharbi regions [11] demonstrated a wide circulation of RVFV vector. The main occupations of the rural population in these regions include animal husbandry. The climate favors mosquito breeding, and malaria transmission continues to affect a large proportion of the population in those areas. An epidemic occurred in the Tagant region in 2012 [3]. Rift Valley fever outbreaks usually occur during rainy seasons when the mosquito population is abundant, and the periods between outbreaks may extend to several decades, during which time it is difficult to establish the diagnosis of RVF cases unless specific epidemiologic and laboratory techniques are used.

In the present report, we analyzed 31 cases over a period of 3 months. Males were more likely to be affected, as previously observed in 2015 [4, 7, 24]. This result can be explained by the fact that men tend to occupy the high risk occupations, such as shepherds and breeders [4, 14–16]. All patients had reported frequent mosquito bites, a direct contact with sick and/or aborted animals or dead animals, and had ingested raw milk frequently. These factors, in addition to socioeconomic and professional activities that involve a direct contact with infected animals, increase their vulnerability to the disease [6, 15, 16]. As with many arboviruses, infection with RVFV is usually asymptomatic, and mild clinical forms last 2 to 6 days. Clinical course is sometimes marked by a rapid weight loss. In most cases, spontaneous recovery occurs rapidly without treatment and without sequelae [6], but severe forms or complications can be observed with various frequencies. Indeed, during the 2015 RVF epidemics, severe forms predominated (81% of cases). The mean duration from the onset of symptoms to hospitalization was 3 days in our study and is in agreement with the literature [4, 6, 14, 15].

The primary site of RVFV replication and tissue pathology is the liver [17, 25]. Liver enzymes are elevated almost constantly to a varying degree [25], and liver failure and hemorrhagic syndrome may result [4, 14, 25]. Neurological signs may appear between 1 and 4 weeks after the onset of symptoms. They are manifested by headaches, confusion, disorientation, focusing signs, meningeal syndrome, or coma [4, 25]. The pathogenesis of brain damage is unclear. The presence of this delay in time to the onset of neurological signs suggests an immunological origin, but the direct cytopathic effect of the RVFV may also contribute to the pathological process [14]. In our study, as previously observed, none of the patients had ocular complications. Symptoms usually appear late, approximately 3 weeks after the onset. They reflect a retinal disease, responsible for vision loss with blind spots [6, 14]. The pathogenesis of the lesions is not well understood, but fluorescein angiography suggests that the lesions are often the result of primary occlusion of the retinal circulation, probably as a result of proliferation of virus particles in the endothelial cells [26].

There is no specific treatment for RVFV infection in humans, and therefore management of clinical cases is only through supportive therapy [4, 6, 17]. The high mortality rate in our study (42%) is comparable to that reported in the literature (25%–45%) [4, 7, 14, 16, 26]. This high mortality rate could be explained by the late medical intervention in hospital, because patients are generally referred to the hospital in an advanced stage of the disease. Hemorrhagic disease is the principal cause of human death due to RVF [4, 16], and it is responsible for up to 50% of deaths [4, 14, 16]. Rift valley fever outbreaks have occurred across eastern

Table 2. Laboratory Parameters of 31 Cases With Severe Rift Valley Fever

Test	Mean ± SD	Reference Range	Range for Patients Assessed
Blood count			
WBC count, 10^3 cells/L	3 ± 3.2	4–10	1–18
Hemoglobin, g/dL	7 ± 2	12–18	3–12
Platelet count, 10^3	60 ± 32	150–400	12–145
Renal function			
Creatinine, µmol	468 ± 333	50–100	44–1098
Urea, mmol	80 ± 50	2.5–6.4	3–201
Liver transaminases			
ALT, U/L	262 ± 384	30–65	28–1530
AST, U/L	235 ± 343	15–37	20–1025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation; WBC, white blood cells.

Africa from 1912 to 2010 approximately every 4–15 years, most of which have not been accompanied by significant epidemics in human populations. Diverse ecological factors influence outbreak frequency, whereas virus evolution has a greater impact on its virulence in hosts. The threat to humans posed by the diversified RVF virus strains increases the potential public health and socioeconomic impacts of future outbreaks [27].

CONCLUSIONS

Given the high risk of mortality related to severe forms of RVF, there is an urgent need to implement management procedures for RVFV-infected patients with designation of a reference center equipped with appropriate medical service and increased vigilance to detect the onset of a possible outbreak of RVF, especially in regions where the climate is suitable and potential vectors exist. These measures will allow a rapid response to an epidemic outbreak among animals or humans to contain possible extension of the disease and ensure improved epidemiological surveillance of RVF.

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