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Bauer, M.P.; Timen, A.; Vossen, A.C.T.M.; Dissel, J.T. van

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Review

Marburg haemorrhagic fever in returning travellers: an overview aimed at clinicians

M.P. Bauer [1], A. Timen [2], A.C.T.M. Vossen [3], J.T. van Dissel [1, *]

[1)] *Department of Infectious Diseases, Leiden University Medical Centre, Leiden, The Netherlands*
[2)] *National Institute for Public Health and the Environment, Bilthoven, The Netherlands*
[3)] *Department Medical Microbiology, Leiden University Medical Centre, Leiden, The Netherlands*

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ABSTRACT

Marburg virus haemorrhagic fever (MARV HF) is a dramatic disease that can occur in a traveller returning from an area where the virus is endemic. In this article, we provide an overview of MARV HF as an imported infection with an emphasis on clinical aspects. Although late features such as rash, signs of haemorrhagic diathesis and liver necrosis may point to the diagnosis, the initial clinical picture is non-specific. If in this early phase the patient's epidemiological exposure history is compatible with MARV HF, the patient should be isolated and managed according to viral haemorrhagic fever protocol and RT-PCR should be performed on the patient's blood as soon as possible to rule out MARV HF (or other possible viral haemorrhagic fevers). In severe cases, direct electron microscopy of blood in specialized centres (e.g. Bernhard-Nocht Institute in Hamburg, Germany) may be considered if the result of the RT-PCR is not readily available. Adequate diagnostics and empirical treatment for other acute life-threatening illnesses should not be withheld while test results are awaited, but all management and diagnostics should be weighed against the risks of nosocomial transmission. **M.P. Bauer, Clin Microbiol Infect 2019;21:e28**

Introduction

Viral haemorrhagic fevers are among the most dreaded travel-related illnesses. Among viral haemorrhagic fevers, filovirus haemorrhagic fevers, caused by the two genera within the *Filoviridae* family, Ebola virus and Marburg virus (MARV), are considered the most lethal. Apart from Ebola Reston virus, which has a reservoir in the Philippines and causes asymptomatic infection in humans, filoviruses are only present in sub-Saharan Africa, where they cause sporadic infections and outbreaks with a high case fatality rate. Only extremely rarely are they acquired by travellers and imported to non-endemic countries. In 2008, we treated a patient who developed Marburg haemorrhagic fever (MARV HF) after a journey to Uganda. The details of this case have been described elsewhere [1,2]. This case has underlined that infectious diseases specialists and clinical microbiologists may encounter MARV HF outside sub-Saharan Africa, so we provide an overview of MARV HF aimed at this specific audience.

The virus

MARV has a non-segmented single-stranded antisense RNA genome and a thread-like appearance with a mean diameter of 91 nm and a mean length of 892 nm [3]. The genus *Marburgvirus* comprises one species, divided in two different viruses (Marburg virus and Ravn virus) whose genomes show at least 79% homology. The genome, consisting of approximately 19 000 bases, encodes seven structural proteins: nucleoprotein (NP), virion protein (VP) 35, VP40, glycoprotein (GP), VP30, VP24 and RNA-dependent RNA polymerase (L). The ribonucleoprotein complex is formed by the genome, NP, VP30, VP35, VP24 and L. The matrix is formed by VP40 and is adjacent to a bilipid envelope derived from the host cell (3). The envelope contains trimeric GP. VP40 is a major virulence factor that blocks interferon signalling [4]. GP is responsible for attachment to an impressively broad array of host cells. No single receptor explaining this pantropism has been identified [5]. After binding, the virus probably enters the cell through macropinocytosis, as has been demonstrated for Ebola virus [6]. Thereafter, the viral and endosomal membrane fuse and the nucleocapsid enters the cytoplasm and catalyses both transcription and replication of the viral genome [7].

* Corresponding author. J.T. van Dissel, Department of Infectious Diseases, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands.
E-mail address: e.j.t.van_dissel@lumc.nl (J.T. van Dissel).

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Epidemiology

Ten separate occurrences of MARV HF had been described (Table 1) (http://www.cdc.gov/vhf/marburg/resources/outbreak-table.html. 2014). The first outbreak to be described occurred in Frankfurt and Marburg, Germany—giving its name to the virus—and Belgrade, Serbia. The source was monkeys imported from Uganda. Laboratory workers who had intensive contact with these animals or their organs were infected. A number of outbreaks have been described since. These outbreaks occurred in Durba and Watsa in the Democratic Republic of the Congo from 1998 to 2000 [8], in Uige, Angola, in 2005 [9], in Kamwenge District, Uganda, in 2007 [10] and in Kabale District, Uganda, in 2012 [11]. Index cases during outbreaks have been associated with underground work in (bat-infested) mines [8,10,12] and visits to bat caves [13–15]. The association with mines and caves and the fact that the disease proved to be rapidly lethal to non-human primates, which were first assumed to be the reservoir, raised suspicion that bats could be a reservoir. This suspicion was reaffirmed when bats of the species *Rousettus aegyptiacus* were shown to harbour and excrete the virus without showing signs of illness [12,16–18]. Our case concerned a tourist who fell ill 13 days after visiting a bat-infested cave, which is longer than the hitherto described incubation time of 3–11 days [14,15,19,20]. After news of our case had reached the public, an American patient who had recovered from an unexplained febrile illness after visiting the same bat-infested cave in Uganda as our patient, requested retesting for MARV HF. Her initial serological tests had been negative, but she had developed IgG antibodies against Marburg virus after her illness and a nested RT-PCR of archived serum taken on day 10 of her illness showed Marburg virus RNA [21]. It is unclear how transmission from the putative bat reservoir to humans occurs. As MARV remains viable for extended periods of time, transmission through direct inoculation of urine or faeces on broken skin or mucous membranes is a possibility. Aerosols have not been shown to play a role in any of the outbreaks. Furthermore, the infection is acquired through manipulation or consumption of mammals found dead in the forest (non-human primates and duikers) and direct contact with blood or haemorrhagic secretions from diseased individuals. It is thought that patients become more infectious during the course of their illness, as haemorrhagic diathesis progresses and bodily fluids contain more blood. One occurrence of sexual transmission from a recovered male patient to his wife during the original Marburg outbreak has been described [20].

The total number of known cases amounts to 465 with an overall case fatality rate of 80% (372) (http://www.cdc.gov/vhf/marburg/resources/outbreak-table.html. 2014). Of note, the fatality rate appears to be lower in patients who acquired the infection through person-to-person transmission, which could possibly be due to a lower inoculum or perhaps mutations rendering the virus less lethal. Also, there are indications that antibody-dependent enhancement may play a role in clinical severity [22].

MARV HF is not a disease that frequently occurs in travellers. To date, only four separate cases have been described (Table 1) [2,14,21]. In our case and the related American case, the patient returned home before falling ill. As many patients visit the cave where these two patients probably acquired MARV HF, the chance of transmission from the natural reservoir must be very small.

Pathogenesis

Progress has been made in understanding the pathogenesis of filovirus infections, mainly from studies of Ebola haemorrhagic fever [23,24], but experimental MARV infections have been studied in non-human primates [25,26]. The primary targets of the virus are dendritic cells, Kupffer cells, monocytes and macrophages, although in the later stages a wide range of cell types can be infected. After intramuscular inoculation in cynomolgus macaques, the virus spreads to liver, spleen and lymph nodes initially, followed by kidney, adrenal gland, lung, pancreas, heart, testis and bone marrow, resulting in variable necrosis, lymphocytic apoptosis and mild neutrophilic and plasmacytic inflammation [26]. Infection of cells can result in necrosis through direct viral cytotoxicity, or, in the case of lymphocytes, in which the virus does not replicate, through apoptosis induced through a mechanism that is as yet unclear [27].

Crucial in the development of MARV HF is deregulation of the innate immune response, resulting in decreased production of interferon-α and interferon-β [28]. In macaques, high levels of pro-inflammatory chemokines and cytokines, such as interferon-α, interleukin-6 and tumour necrosis factor-α, are observed from day 6 after inoculation [25,26]. It is hypothesized that the timing of the appearance of pro-inflammatory cytokines is crucial and that a delayed adaptive immune response with concomitant cytokine storm is associated with death [29]. Stephan Günther and co-workers at Bernhard Nocht Institute for Tropical Medicine (Hamburg, Germany) were able to determine in retrospect day-to-day cytokine levels in our patient and found a pattern compatible with this hypothesis [2]. An early peak in the anti-inflammatory cytokine interleukin-10 was followed by a peak in interferon-γ and tumour necrosis factor-α on day 7 of the illness, and subsequently a peak in interleukin-6 with peaks in markers of endothelial dysfunction. This latest peak occurred on day 9, just before death. Infected dendritic cells are incapable of maturing and activating co-stimulatory molecules, which leads to an incapacitated adaptive immune response [30]. In an animal model of MARV HF, peripheral blood $CD4^+$ and $CD8^+$ T-cell counts remained normal, whereas the percentage of splenic $CD8^+$ T cells declined. Furthermore, the number of circulating B cells and double-positive T cells increased [25].

Table 1
Epidemiological characteristics of cases of Marburg haemorrhagic fever that have been described

Year	Country	No. of cases	Fatality rate	Activity of primary cases
1967	Germany and Yugoslavia ex Uganda	31	23	Handled diseased monkeys in laboratory
1975	South Africa ex Zimbabwe	3	33	Traveller; imported infection from country of source
1980	Kenya	2	50	Visited cave
1987	Kenya	1	100	Traveller; visited cave
1990	Russia	1	100	Worked in laboratory
1998–2000	Democratic Republic of Congo	154	83	Worked in mine
2004–2005	Angola	252	90	Unknown
2007	Uganda	4	25	Worked in mine
2008	USA ex Uganda	1	0	Traveller; visited cave; imported infection from country of source
2008	Netherlands ex Uganda	1	100	Traveller; visited cave; imported infection from country of source
2012	Uganda	15	27	Unknown

The result of the above-mentioned processes is a syndrome resembling septic shock with vascular dysfunction, disseminated intravascular coagulation and eventually multi-organ failure. Extensive necrosis of organs, especially the liver, may occur. Liver necrosis is usually presumed not to be directly accountable for death, although in our case, hepatic encephalopathy may well have been the cause of death [2].

Clinical presentation

The clinical symptoms and signs of MARV HF have been described in a number of well-documented cases and case series [2,13–15,19,20,31] and are listed in Table 2. Non-specific flu-like symptoms develop in the first week, including fever with a relative bradycardia, chills, headache, general malaise, anorexia, sore throat, dry cough, chest, back, joint and muscle pain, followed by nausea, vomiting and diarrhoea. Leucopenia with a left shift of the granulocytes and thrombocytopenia can be seen at presentation. Abnormal lymphocytes and pseudo-Pelger cells were seen in blood smears in the first two outbreaks of MARV HF [19,20]. In our patient, erythroblasts were seen in the blood [2]. In half of the patients a non-itching conjunctival injection or haemorrhage is present. In Caucasian patients on days 5 to 7 a non-pruritic, maculopapular or morbilliform rash or pinhead dark red papules around the hair follicles can be noted over the thorax and extremities, spreading over the whole body. Around the same time, vascular instability with shock and renal failure may develop. Lymphadenopathy may be found. Increased liver enzymes (aspartate transaminase > alanine transaminase) and liver failure may develop with right sided upper abdominal pain or tenderness, resulting in coagulopathy, hypoalbuminaemia, hypoglycaemia, lactic acidosis, hyperammonaemia and hepatic encephalopathy. Jaundice is uncommon. Features of haemorrhagic diathesis may develop, most often oozing from puncture sites, gums, nose and gastrointestinal tract. Neurological symptoms include lethargy, drowsiness and dysaesthesias. Interestingly, our patient mentioned hearing loss, a feature associated with Ebola haemorrhagic fever [32], although this may also have been caused by high levels of mefloquine due to decreased hepatic metabolism. Furthermore pancreatitis [2] and pericarditis [20] have been associated with MHF. In fatal cases, patients usually die in the second week of the illness. Survivors start to recover 2 weeks after onset of disease. Orchitis [20] and uveitis [19] have been described as late complications.

Table 2
Clinical and laboratory features of Marburg haemorrhagic fever

Clinical features
Fever, chills, relative bradycardia
Headache
General malaise, anorexia
Sore throat, dry cough, chest, back, joint and muscle pain
Nausea, vomiting and diarrhoea
Lymphadenopathy
Right upper abdominal pain or tenderness
Conjunctival injection
Maculopapular or papular rash (from day 5)
Mucosal bleeding, oozing from puncture sites
Septic shock
Lethargy, drowsiness and dysaesthesias
Hepatic encephalopathy
Orchitis (late complication)
Uveitis (late complication)
Laboratory features
Leucopenia
Granulocyte left shift
Abnormal lymphocytes
Pseudo-Pelger cells
Erythroblastosis
Thrombocytopenia
Elevated creatinine
Elevated liver enzymes (AST > ALT)
Coagulopathy
Hypoalbuminaemia
Hypoglycaemia
Lactic acidosis
Hyperammonaemia
Elevated creatine kinase

Outbreak control

Patients with possible MARV HF should be isolated according to viral haemorrhagic fever protocol as soon as the diagnosis is considered, and appropriate measures must be taken. Naturally, when a patient presents with signs of haemorrhagic diathesis within the incubation period after visiting an endemic area, MARV HF will probably be considered. However, the initial clinical picture of MARV HF is non-specific. For instance, in our patient, a whole spectrum of possible aetiological infections were considered initially, including malaria, typhoid fever, leptospirosis, rickettsiosis, dengue fever and several other viral diseases. Only when acute liver failure developed did focus turn to MARV HF [2]. It is practically impossible to strictly isolate every patient who develops a non-specific febrile illness within the incubation period after returning from an area endemic for MARV HF. Therefore, one must rely on epidemiological clues, such as contact with patients or diseased animals or their body fluids. We suggest that visits to bat-infested caves or mines be regarded as a risk factor, too. The CDC recommend the following minimal biosafety/biocontainment measures in MARV HF, also aimed at resource-poor settings [33]. The patient must remain in a low-air-pressure isolation room with separate toilet and leave this room only if strictly necessary. There should be a separate anteroom for personnel to change clothes. All hospital personnel entering the patient's room must wear disposable gowns, gloves, FFP2 masks and—in case of risk of infectious body fluids infecting hospital personnel's eyes, e.g. in the case of vomiting or diarrhoea—protective eyeglasses. Blood samples are taken only if absolutely necessary by means of a closed system and then preferably analysed at point-of-care. If this is impossible, samples must be transported to the microbiological laboratory by a dedicated courier where they are subsequently inactivated in a biosafety level 3 laboratory by heat (1 h at 60°C) or chaotropic salt (guanidine isothiocyanate) and next distributed to other laboratories. All waste should be collected in a separate room and burnt. All other non-disposable material that leaves the patient's room should be cleaned with soap and disinfected with bleach. If the patient dies, the body should be sprayed with bleach, sealed in a mortuary sack which is also sprayed with bleach and buried. The body with mortuary sack may be sealed in a second mortuary sack. Furthermore, all relevant authorities must be informed as soon as the suspicion of MARV HF rises. Contact lists should be kept.

The public health response to our case has been described in detail elsewhere [1]. Basically, all contacts of the patient should take their temperature twice daily for up to 3 weeks after last contact with the index case and report daily to the public health officers, and be put in quarantine if a fever develops (two measurements $\geq$38.3°C), awaiting confirmation or refutation of MARV HF or another diagnosis. As yet, there is no commercially available vaccine, although vaccination by means of a recombinant vesicular stomatitis virus vector expressing MARV GP is being investigated for pre-exposure [34] and post-exposure [35] prophylaxis. In patients who survive, persistence of MARV in various body fluids must be investigated and isolation must be adapted accordingly. Recovered male patients should practice safe sex as long as

persistence of MARV in semen has not been ruled out. It is unknown whether MARV can also be transmitted sexually from recovered women to men.

Diagnosis and treatment

During clinical illness and possibly the incubation period, MARV RNA is detectable in blood samples by RT-PCR. In addition, ELISAs, assumed to be less sensitive, may demonstrate antigen in body fluids. In our patient, who had a constant plasma viral load between 107 and 108 copies/mL, the virus was readily detectable by electron microscopy [2]. This technique may possibly lead to a faster diagnosis than PCR in severely-ill patients with high viral loads (Stephan Günther, personal communication). Patients who die usually do not develop an antibody response. In patients who survive, IgM is demonstrable in serum in the first week of illness, shortly followed by IgG [31].

So far, there has been no causal treatment for MARV HF and only supportive care can be given. Our patient died in spite of maximum supportive care on a state-of-the-art intensive care unit, including mechanical ventilation, vasopressor and inotropic support, correction of severe electrolyte imbalances, transfusion of thrombocytes, erythrocytes and fresh frozen plasma, continuous venovenous haemofiltration in combination with a molecular absorbent recirculation system and administration of mannitol and hypertonic saline to counter raised intracranial pressure [2]. Theoretically, patients might benefit from treatment with interferon-α, although evidence is lacking.

Conclusions

MARV HF continues to be one of the most serious infections known to man, with a high case fatality rate, even in settings where maximum supportive care can be given. Though a rare event, MARF HF may be imported to countries outside sub-Saharan Africa. Therefore, it is important that clinicians are aware of the epidemiology and clinical presentation of this disease. Hospitals that treat patients returning from sub-Saharan Africa should have a viral haemorrhagic fever protocol aimed at minimizing the risk of nosocomial transmission while at the same time providing maximum care and making a definitive diagnosis as soon as possible.

Transparency declaration

The authors declare that they have no conflicts of interest.

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