Available online at www.sciencedirect.com
ScienceDirect
Antiviral Research 78 (2008) 103–115
Antiviral Research
www.elsevier.com/locate/antiviral

New opportunities for field research on the pathogenesis and treatment of Lassa fever

Sheik Humarr Khan [a,b], Augustine Goba [a,b], May Chu [c], Cathy Roth [c], Tim Healing [c], Arthur Marx [c], Joseph Fair [b,d], Mary C. Guttieri [d], Philip Ferro [d], Tiffany Imes [b], Corina Monagin [b], Robert F. Garry [b], Daniel G. Bausch [b,*],

for the Mano River Union Lassa Fever Network [1]

[a] *Kenema Government Hospital, Ministry of Health and Sanitation, Kenema, Sierra Leone*
[b] *Tulane University Health Sciences Center, New Orleans, LA, United States*
[c] *World Health Organization, Geneva, Switzerland*
[d] *United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, United States*

Received 5 September 2007; accepted 6 November 2007

Abstract

Unlike many viral hemorrhagic fevers (VHFs), Lassa fever (LF) is not a rare disease that emerges only as sporadic cases or in outbreak form. Although surveillance is inadequate to determine the true incidence, up to 300,000 infections and 5000 deaths from LF are estimated to occur yearly. The highest incidence is in the "Mano River Union (MRU) countries" of Sierra Leone, Liberia, and Guinea. Although civil unrest in this region over the past two decades has impeded capacity building and research, new-found peace in recent years presents new opportunities. In 2004, the Mano River Union Lassa Fever Network (MRU LFN) was established to assist MRU countries in the development of national and regional surveillance, diagnosis, treatment, control, and prevention of LF. Here, we review the present literature on treatment and pathogenesis of LF and outline priorities for future research in the field made possible by the improved research capacity of the MRU LFN.

Keywords: Lassa virus; Lassa fever; Arenavirus; Viral hemorrhagic fever; West Africa; Antiviral therapy; Ribavirin; Pathogenesis

1. Introduction

Lassa fever (LF) is an acute and sometimes severe viral hemorrhagic illness caused by Lassa virus (LASV), a member of the family *Arenaviridae* (Enria et al., 2006). LF is endemic in parts of West Africa, where up to 300,000 cases and 5000 deaths occur yearly (McCormick et al., 1987b). Humans contract LF primarily through contact with contaminated excreta of rodents of the genus *Mastomys*, which is the natural reservoir (Monath et al., 1974b; McCormick et al., 1987b). Secondary transmission of LASV between humans occurs through direct contact with infected blood or bodily secretions (Enria et al., 2006). Nosocomial transmission and outbreaks have been described in healthcare facilities in endemic areas (Carey et al., 1972; Monath et al., 1973; Fisher-Hoch et al., 1995; WHO, 2005).

2. History of research on Lassa fever in West Africa

Although LF was first recognized in Nigeria in 1969 (Buckley and Casals, 1970; Frame et al., 1970; Troup et al., 1970), field studies in the wake of hospital outbreaks soon revealed the MRU countries of West Africa (Sierra Leone, Liberia, and Guinea) to have the highest incidence of the disease (Monath et al., 1973, 1974a; Fraser et al., 1974; Knobloch et al., 1982; McCormick et al., 1987a,b; Lukashevich et al., 1993; Bausch et al., 2001) (Fig. 1). The problem was particularly severe in eastern Sierra Leone, prompting the Centers for Disease Control and Prevention (CDC) to establish a laboratory and research and control program there in 1976, which subsequently provided the majority of our present-day scientific knowledge on LF (McCormick

* Corresponding author at: Tulane School of Public Health and Tropical Medicine, Department of Tropical Medicine, SL-17, 1430 Tulane Avenue, New Orleans, LA 70112-2699, United States. Tel.: +1 504 988 6368; fax: +1 504 988 6686.
E-mail address: dbausch@tulane.edu (D.G. Bausch).
[1] See Appendix A for the list of members.

0166-3542/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2007.11.003

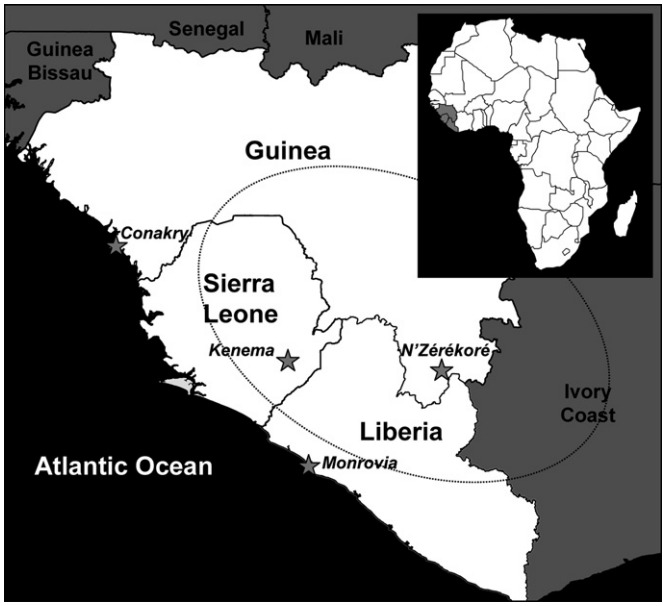

Fig. 1. Map of the Mano River Union countries (Sierra Leone, Guinea, and Liberia). The approximate known endemic area for Lassa fever is shown by the dotted oval. Sites of the four laboratories included in the Mano River Union Lassa Fever Network are indicated by stars and consist of the Kenema Government Hospital Lassa Laboratory in Kenema, Sierra Leone; the Central Public Health Laboratory Service in Monrovia, Liberia; the Program on Hemorrhagic Fevers in Conakry, Guinea; and the International Center for Research on Tropical Infections in N'Zérékoré, Guinea.

et al., 1987b). The program was based at Kenema Government Hospital (KGH) in the heart of the LF endemic area and included the establishment of a treatment ward and diagnostic laboratory (Bausch et al., 2004).

Civil war in Sierra Leone forced suspension of the CDC program in 1993, with subsequent transfer of the public health aspects to the relief organization Merlin (http://www.merlin.org.uk/) in 1996. The laboratory was not continued. Civil war also scuttled what had been an active research program in neighboring Liberia during this era (Mertens et al., 1973; Monath et al., 1973; Bloch, 1978; Frame et al., 1979, 1984a,b; Knobloch et al., 1980, 1982; Monson et al., 1984, 1987; Yalley-Ogunro et al., 1984; Van der Waals et al., 1986; Frame, 1989). Research on LF by various investigators has continued in neighboring Guinea (Lukashevich et al., 1993; ter Meulen et al., 1996, 1998; Bausch et al., 2001; Demby et al., 2001; Fair et al., 2007; Fichet-Calvet et al., 2007), but the apparent lower incidence of human disease (for unclear reasons) in that country has precluded extensive investigations on pathogenesis, clinical disease, and treatment. In fact, no studies have been published on treatment interventions for LF in the last 20 years.

3. Pathogenesis

The history of civil unrest and undeveloped biomedical infrastructure in the endemic area for LF, the relative danger of conducting full post-mortem exams on the bodies of patients who died of the disease, and certain African cultural taboos on manipulation of corpses have prevented extensive study of the pathogenesis and pathology of LF in humans. Our present understanding is thus based on the limited data from humans (Ikerionwu et al., 1978; Walker et al., 1982) combined with cautious extrapolation from extensive observations made in the excellent model of LF in non-human primates (Gowen and Holbrook, 2008).

The pathogenesis of LF appears to be related to unchecked viremia (Johnson et al., 1987). LASV is cleared rapidly in survivors. Cell mediated immunity appears to be the most important arm in recovery (Jahrling et al., 1985a; Peters et al., 1987). The humoral response often lags, with neutralizing antibodies typically appearing after recovery in survivors and not at all in most fatal cases (Johnson et al., 1987; Bausch et al., 2000). LASV infection probably results in life-long immunity, at least against severe disease, although this question has not been extensively studied in humans (McCormick et al., 1987b).

Microvascular instability and impaired hemostasis are the pathophysiologic hallmarks of LF and the VHFs (Enria et al., 2006). Contrary to popular thought, mortality does not usually result from exsanguination or direct virus-induced necrosis, although mild-to-moderate necrosis may be noted, especially in the liver and spleen (Callis et al., 1982; Walker et al., 1982). Rather, severe disease appears to result from the interaction of LASV with macrophages and dendritic cells, either directly or indirectly via soluble mediators, resulting in a process akin to septic shock, with activation of a host of inflammatory and vasoactive mediators leading to cellular dysfunction, insufficient effective circulating intravascular volume, and multi-organ system failure (Liu et al., 1986; Peters et al., 1987; Roberts et al., 1989; Guo et al., 1992, 1993; Qian et al., 1992; Aronson et al., 1995; Fennewald et al., 2002). One small study of LF in humans, however, found a lack of stimulation of various cytokines to correlate with a poor outcome (Mahanty et al., 2001). Data from animal models suggest that cardiac inotropy may be directly or indirectly inhibited, further impairing organ perfusion (Qian et al., 1994).

Dendritic cells and cells of the macrophage-monocyte line appear to be the primary initial sites of LASV replication after inoculation in animal models. After replication in the local tissues and regional lymph nodes, LASV is disseminated through lymph and blood monocytes to a wide variety of organ parenchyma and their associated mesothelial cell linings, including the liver, spleen, endothelium, lymph nodes, kidney, adrenal gland, pancreas, placenta, uterus, breast, and gonads (Jahrling et al., 1980; Callis et al., 1982; Walker et al., 1982). Inflammatory cell infiltrates are usually mild, consisting of a mix of mononuclear cells and neutrophils (Walker et al., 1982). Adrenal or pituitary gland necrosis with consequent vascular collapse has been postulated but not specifically demonstrated (Walker et al., 1982). Although mild thrombocytopenia typically occurs, hemorrhage appears to be primarily attributable to LASV-induced release of a soluble mediator impairing platelet aggregation (Cummins et al., 1989b). There is no evidence for a role of immune complexes, complement activation, or DIC as relevant pathogenic mechanisms in LF (Lange et al., 1985).