

# CENTRAL NERVOUS SYSTEM DISEASE ASSOCIATED WITH MAJOR VIRAL HAEMORRHAGIC FEVER VIRUSES OF PUBLIC HEALTH IMPORTANCE: CHALLENGES IN PATIENT DIAGNOSIS, EVALUATION, AND MANAGEMENT IN RESOURCE-LIMITED SETTINGS

\*Peter O. Okokhere,<sup>1,2</sup> Mojeed O. Rafiu,<sup>1</sup> Idowu A. Bankole<sup>1</sup>

1. Department of Medicine, Irrua Specialist Teaching Hospital, Irrua, Nigeria

2. Institute of Lassa Fever Research and Control, Irrua Specialist Teaching Hospital, Irrua, Nigeria

\*Correspondence to okokherep@gmail.com

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## ABSTRACT

Viral haemorrhagic fever (VHF) viruses cause infectious diseases that are of public health importance. Billions of people from all over the world are at risk of exposure to infection from these viruses with epidemics or outbreaks occurring in both endemic and non-endemic areas. The VHF viruses are largely neglected but are re-emerging as real threats to global health. While the more dramatic clinical presentations (such as bleeding and vascular collapse) are well known, the contribution of features that involve the central nervous system (CNS) to mortality and morbidity are not fully recognised. The diagnosis of VHF in febrile patients with CNS-related features, but who do not present with characteristic bleeding, may be missed or delayed because of a low index of suspicion. The proper evaluation of such patients with CNS disease is hampered by the dearth of neurologists and investigational tools, and weak health systems in resource-limited settings where most of the VHF viruses are endemic. Addressing these constraints would require investment in capacity building and infrastructural development in the affected countries.

**Keywords:** Viral haemorrhagic fever (VHF) viruses, central nervous system (CNS), mortality, morbidity, evaluation, constraints, resource-limited settings.

## INTRODUCTION

Viral haemorrhagic fever (VHF) viruses are a group of single-stranded RNA pathogens that largely produce acute febrile syndromes that may include bleeding from mucosal and other body surfaces in affected individuals. The VHF viruses of public health importance are usually associated with multi-organ dysfunction that may involve the central nervous system (CNS) in severe cases, with consequent increases in morbidity and mortality.

Outbreaks of cases may occur both in endemic<sup>1,2</sup> and non-endemic areas.<sup>3-6</sup> As a group, the VHF viruses contribute significantly to the overall global disease burden<sup>7-13</sup> and have a negative socio-economic impact on the lives of the people in the affected communities. Some of the viruses may

even be used for bioterrorism.<sup>14</sup> Unfortunately, these viruses and the diseases they cause have remained largely neglected, leading to avoidable suffering among the people of the regions where they are endemic. Significant responses to VHF outbreaks get national or international attention usually only when a severe epidemic or pandemic occurs, as was the case with recent Ebola virus disease (EVD) in West Africa. Even then, the global response was slow in coming,<sup>4</sup> which likely contributed to the severity of the outbreak and the consequent huge human and economic toll that ensued.

The many sporadic cases of VHF, with varying degrees of clinical severity, are generally under-reported. These aggregate to assume significance in terms of the annual total number of cases

and the morbidity that may occur. For example, it is well known that even subclinical or mild Lassa fever infection can lead to sensorineural hearing loss of varying degrees of severity,<sup>15</sup> leading to educational and socio-economic implications. There is little or no assessment of the true burden of hearing impairment due to Lassa fever in all the areas endemic with the disease, even though estimates put the occurrence of hearing disability attributable to Lassa fever at about one-third of infected patients.

The VHF viruses, especially Lassa fever and Ebola, are rarely mentioned as important causes of CNS disease in the literature. This may be because of a paucity of information, partly due to incomplete evaluation of affected patients and the under-reporting of cases that are not associated with bleeding. The recent outbreak of EVD in West Africa illustrates the difficulties encountered in the proper evaluation of patients with VHF.<sup>3</sup> However, many studies,<sup>16-19</sup> including the recent ones on EVD,<sup>20,21</sup> indicate that VHF viruses are aetiological agents of CNS disease. This paper discusses the contribution of VHF to CNS disease, highlighting the spectrum of CNS manifestations, and the challenges encountered in the diagnosis, evaluation, and treatment of patients who present with CNS features in resource-limited settings.

## BRIEF OVERVIEW OF NEUROLOGICAL FEATURES OF VIRAL HAEMORRHAGIC FEVERS OF PUBLIC HEALTH IMPORTANCE

### Ebola Virus Disease

The main clinical features of this disease are vomiting and diarrhoea.<sup>3,4,22,23</sup> CNS features include encephalopathy, acute meningitis, meningoencephalitis complicated by cranial neuropathies, and radiculopathy.<sup>20</sup> The mechanism of neurological disease may be metabolic, immune-mediated, or neurocytopathic.<sup>20,21,24,25</sup>

### Marburg Viral Haemorrhagic Fever

Neurological features may occur in the severe stage of the disease, and consist of irritability, confusion, and aggression.<sup>26</sup> The mechanism of CNS disease may include electrolyte imbalance and metabolic encephalopathy from liver and renal failure.

### Lassa Fever

A spectrum of neurological manifestations occurs in different phases of the illness.<sup>16-18,27-32</sup>

This includes aseptic meningitis, sensorineural deafness, encephalitis, encephalopathy, ataxia, and subacute or chronic neuropsychiatric syndromes. Coexistence with malaria leads to an increased frequency of CNS features.<sup>16</sup> Metabolic,<sup>29,30</sup> direct neurocytopathic,<sup>18,28</sup> or immunologic<sup>15,29</sup> are possible pathogenetic mechanisms of CNS disease.

### Dengue Fever

Neurological features, the mechanisms of pathogenesis which include direct neurotropic effect, metabolic derangement, and post-infectious immune-mediated processes, may involve all parts of the nervous system, and include clinical manifestations such as headache, insomnia, irritability, encephalopathy, seizure, encephalitis with focal neurological deficit, motor deficit, myelitis, encephalomyelitis, myositis, polyradiculoneuritis, neuromyelitis optica, mononeuropathy, polyneuropathy, altered levels of consciousness, and stroke.<sup>33-35</sup>

### Rift Valley Haemorrhagic Fever

CNS disease in Rift Valley Haemorrhagic Fever includes features such as retro-orbital headache, temporal visual loss without retinopathy, retinitis, visual hallucinations, nuchal rigidity, meningeal irritation, confusion, seizure, hyperreflexia, ataxic gait, blindness, quadriparesis, transient alteration in level of consciousness, stupor, coma, hypersalivation, teeth-grinding, locked-in syndrome, and choreiform movement of upper limbs.<sup>36,37</sup> The mechanism of CNS disease is cytopathic, with the brains of patients showing areas of focal necrosis with infiltrates of mainly lymphocytes and macrophages, and perivascular cuffing on histology.<sup>36</sup>

### Crimean-Congo Haemorrhagic Fever

Neurological features include nuchal rigidity, confusion, irritability, mood swings, lassitude, and depression.<sup>38</sup> The pathogenetic mechanism of CNS disease may be metabolic as a consequence of liver and renal failure, leading to encephalopathy.<sup>38</sup>

### Argentine Haemorrhagic Fever

Neurological features associated with Argentine haemorrhagic fever include tremors of the tongue and upper extremities, cerebellar signs, and confusion.<sup>10,39</sup> However, cerebrospinal fluid (CSF) findings may be normal.<sup>39</sup> The mechanism of the cerebellar signs occurring in the convalescent period may be immune-mediated.<sup>40</sup>

## Omsk Haemorrhagic Fever

CNS manifestations occur following a relapse in 30–50% of cases with this disease. Common CNS features include permanent headache and meningism; permanent but rare CNS complications are hearing loss and behavioural, psychological, or psychiatric challenges associated with neurological dysfunction.<sup>12</sup> The mechanism of CNS disease is considered to be neurocytopathic with associated severe breaching of the blood-brain barrier in some cases.<sup>12</sup>

## Yellow Fever

CNS manifestations of yellow fever include headache, agitation, delirium, convulsions, stupor, and coma. These features are probably due to metabolic encephalopathy resulting from extensive hepatic necrosis and renal failure, even though brain oedema, increased CSF pressure, and elevated CSF protein may be seen in severe cases.<sup>41</sup>

### EVALUATION OF PATIENTS WITH CENTRAL NERVOUS SYSTEM INFECTIONS DUE TO VIRAL HAEMORRHAGIC FEVER VIRUSES

The clinical evaluation of the patients with CNS infectious disease due to VHF viruses begins with an analysis of the patient's history, followed by a detailed physical examination when practicable. Fever, headaches, and neck stiffness without a significantly altered level of consciousness would suggest aseptic meningitis, while abnormal behaviour, confusion, seizures, and significantly altered mental status, in addition to fever and headache, would increase the likelihood of encephalitis. A physical examination finding of nuchal rigidity is a classic feature of meningeal irritation, and the presence of Kernig's and Brudzinski's signs may add support to the clinical impression of meningitis. In viral encephalitis, physical examination may reveal confusion, disorientation, irritability, ataxia, tremors, varying degrees of profound altered levels of consciousness, and focal neurological deficits.

If there are no contraindications for lumbar puncture, a CSF sample should be obtained and examined for its physical, biochemical, and microbiological characteristics. The essential CSF findings for both aseptic meningitis and encephalitis caused by viruses include pleocytosis (mainly mononuclear cells), normal or decreased

glucose levels, and normal or increased protein levels; Gram's stain is negative and culture is sterile. Further evaluation of the CSF would be determined by the prevailing epidemiological characteristics, and may include CSF polymerase chain reaction (PCR), serology, and viral culture (Table 1). Blood culture, serum serology, and blood PCR may be relevant depending on the suspected aetiological agent.

In addition, a patient with suspected acute viral encephalitis should undergo neuroimaging and electroencephalogram examinations to distinguish between focal or diffuse abnormalities of brain parenchymal involvement. In some instances of viral encephalitis, neuroimaging may be normal. If CSF PCR is not diagnostic and the patient's clinical status continues to deteriorate, with magnetic resonance imaging (MRI) scans showing focal parenchymal involvement, a brain biopsy may be justified to make a definitive diagnosis, and guide specific treatment.<sup>42</sup>

Relevant investigations to exclude metabolic disturbance, haematological abnormalities, sepsis, and fluid or electrolyte imbalance include full blood and differential counts, erythrocyte sedimentation rates, C-reactive protein, blood sugar, serum electrolytes, urea and creatinine, liver function tests, blood cultures, serum amylase, and urine analysis. It is important to remember that both encephalopathy and encephalitis can coexist.

While evaluating VHF CNS infections, especially when bleeding is not a feature, important differential diagnoses of infectious origin are the same for non-VHF causes, and include partially treated bacterial meningitis, herpes viral encephalitis, lymphocytic choriomeningitis virus infection, mycobacteria, neurosyphilis, *Listeria spp.*, *Brucella spp.*, *Mycoplasma spp.*, *Coxiella spp.*, *Rickettsia spp.*, *Leptospira spp.*,<sup>42</sup> and malaria, causing conditions that, when diagnosed, have effective treatments.

### MANAGEMENT OF VIRAL HAEMORRHAGIC FEVERS

Suspected and confirmed cases should be managed in isolation facilities where care should be taken to prevent truly negative cases from eventually becoming infected by laboratory confirmed patients. For all VHF, supportive care is important and may be the only treatment option. Fluid and electrolyte replacement, including blood transfusion when indicated, are essential.<sup>2</sup>

**Table 1: Viral haemorrhagic fevers with relative frequencies of bleeding and central nervous system features.<sup>1</sup>**

Family	<i>Arenaviridae</i>					<i>Bunyaviridae</i>			<i>Filoviridae</i>		<i>Flaviviridae</i>				
	LF	ArHF	BoHF	BrHF	VeHF	CCHF	HHFRS	RVF	EVD	MHF	ALHF	DHF	OHF	KFD	YF
Virus	LF	Junin	Machupo	Sabia, Flexal v	Guanarito	CCHF	Hantaan	RVF	Ebola	MHF	ALHF	Dengue	OHF	KFD virus	YF virus
Incubation period (days)	5-21	7-14				3-12	9-35	2-5	2-21		3-8	3-15	3-8	3-8	3-6
Bleeding	1+	3+				3+			2+		2+				3+
CNS manifestations	1+	3+				1+	1+	2+	1+		2+	1+	3+	3+	2+
CFR (%)	10-20	15-30 (untreated cases)				15-30	5-15	50	25-90	28-80	1-3	10-15 (untreated cases)	0.4-2.5	1-3	20-50

1+ = not frequent; 2+ = frequent; 3+ = more frequent.

VHF: viral haemorrhagic fever; LF: Lassa fever; ArHF: Argentine haemorrhagic fever; BrHF: Brazilian haemorrhagic fever; BoHF: Bolivian haemorrhagic fever; VeHF: Venezuelan haemorrhagic fever; CCHF: Crimean-Congo haemorrhagic fever; HHFRS: Haatan haemorrhagic fever with renal syndrome; RVF: Rift Valley haemorrhagic fever; EVD: Ebola virus disease; MHF: Marburg haemorrhagic fever; ALHF: Alkhumra haemorrhagic fever; DHF: Dengue haemorrhagic fever; OHF: Omsk haemorrhagic fever; KFD: Kyasamur forest disease; YF: yellow fever; CNS: central nervous system; CFR: case fatality rate.

Specific therapy is available for some VHF. The antiviral drug ribavirin shows varying degrees of effectiveness against the Lassa virus, Junin virus, Hantaan virus, Rift Valley haemorrhagic fever virus, and Crimean-Congo haemorrhagic fever virus; ribavirin is particularly effective in Lassa fever when administered within 6 days of the onset of the illness.<sup>43</sup> The use of commercially produced human monoclonal antibodies and novel experimental drugs have shown promise in the treatment of EVD<sup>20,44</sup> and may be the mainstay of specific treatment in the near future. The administration of convalescent serum is indicated in Argentine viral haemorrhagic fever,<sup>10</sup> and has been found to be useful against other VHF viruses,<sup>20,44</sup> especially in those without specific antiviral therapy. It was the only effective means of treating VHFs in the past,<sup>12,45</sup> and still has relevance today.<sup>20</sup>

Multi-organ disease would require management in intensive care settings where appropriately trained medical staff are available. The EVD survivors infected in West Africa during the recent Ebola outbreak, and treated in the UK and USA, have shown that even in patients with very severe disease, survival is possible when the appropriate infrastructure and medical expertise are available.<sup>20,44</sup>

### Prevention and Control Measures

Knowledge of the vector(s)/host(s) and the mode(s) of transmission of the specific virus provide

strategies for prevention. For the VHF viruses, avoiding primary or secondary exposure is of paramount importance. Once an index case is identified, standard infection control measures must be started immediately.<sup>46</sup>

Isolation of infected humans in well-equipped and staffed designated isolation facilities is ideal. The education and re-education of healthcare personnel on measures to prevent nosocomial infections cannot be overemphasised. Post-exposure prophylaxis may be applicable, for example in Lassa fever exposure.<sup>47</sup> Vector control measures applied appropriately may reduce the rates of transmission and disease. Unfortunately, many VHF viruses currently do not have effective vaccines against them; effective vaccines are available for yellow fever, Omsk haemorrhagic fever, and Dengue fever. The devastating consequences of the recent EVD in West Africa has made urgent development of effective vaccines against the VHF viruses of public health importance imperative.

### Challenges in Diagnosis, Evaluation, and Treatment

Late presentation to hospital is a common phenomenon in resource-limited areas. The varied and non-specific nature of the early stages of these viral diseases with early symptoms and signs shared by common endemic diseases,<sup>1</sup> the penchant for self-medication, the patronage of

patent medicine sellers, the use of traditional remedies, the consultation with faith healers, the scarce number of healthcare facilities in rural communities, the difficulty in accessing the available healthcare facilities, and the myths and false perceptions surrounding these diseases, all contribute to late presentation that leads to increased mortality and morbidity. CNS diseases typically occur in the late stages of VHF illnesses.

The non-specific nature of the clinical features of most VHFs makes early clinical diagnosis difficult, thus requiring a high index of suspicion. In some instances, even in late stages of the disease, bleeding may not be a clinical feature. Many patients may be treated first for malaria, and common causes of diarrhoea, resulting in delay in early diagnosis, and the potential for nosocomial spread if preventive control measures are not observed routinely.<sup>48,49</sup> Early case recognition, rapid laboratory diagnosis, and early commencement of supportive and specific therapies, where applicable, may improve prognosis.<sup>3</sup>

Furthermore, bleeding is not present in all cases of VHF,<sup>1</sup> and is also not specific for VHF. Strain variation of the virus in different regions of the world and within individual countries, coupled with host factors, may influence the clinical features in different areas, and may not allow for generalisation in the application of clinical diagnostic criteria. Unfortunately, even in areas endemic for VHF, many healthcare workers may not be familiar with the clinical features of the major VHF, particularly when bleeding is absent, resulting in missed or delayed clinical diagnosis.<sup>49</sup> This may result in devastating consequences to patients and healthcare workers.<sup>45,50</sup> Healthcare workers must be familiar with the existing diagnostic criteria while efforts at improving them continue. VHF should be in the curriculum of medical education in Africa and other regions where outbreaks occur; practising healthcare professionals should be encouraged to have continued medical education on VHF.

Even though good progress has been made in the development of local infrastructure and manpower in West Africa, the number of available laboratories capable of effectively making a definitive diagnosis of VHF is still grossly inadequate.<sup>9,51</sup> More laboratories, including well-equipped mobile laboratories that can be deployed to outbreak areas quickly, are needed. It is also of critical importance to urgently develop rapid diagnostic

test kits effective in making field or bedside diagnosis of VHFs. Fortunately, a rapid diagnostic test has been shown to be effective in diagnosing Lassa fever in Sierra Leone.<sup>51</sup> It is hoped that this breakthrough achievement can be replicated with other VHFs.

Of concern is the highly contagious nature and high fatality rates associated with some of the major VHF, which may pose limitations to the evaluation of infected patients, as it might be too risky for researchers or clinicians to conduct full clinical evaluation and use modern investigational tools. Even where the opportunity is present for better evaluation, especially for viruses with relatively low secondary infectivity rates, the lack of infrastructural and manpower resources in resource-poor countries is a serious hindrance.<sup>3</sup>

The apparent global neglect of these re-emerging diseases has delayed the development of effective vaccines against most of the VHF viruses of public health importance. The recent EVD outbreak in West Africa showed clearly how unprepared the world is in responding to significant outbreaks of severe VHF epidemics. Perhaps financial considerations may partly explain why pharmaceutical companies are probably not keen on putting resources into vaccine development. The fact that most of the VHFs are in developing countries may also contribute to the palpable apathy towards intensive VHF vaccine research.

## DISCUSSION

Many studies<sup>10,16-18,24,25,27-29,31,33-39,41</sup> have attempted to elucidate the varied CNS manifestations occasioned by VHF virus infection in the acute, convalescent, and long-term phases of illness. However, the recent outbreak of EVD in West Africa, and the subsequent post-infectious CNS syndromes<sup>20,21</sup> encountered show that the clinical spectrum of EVD as it relates to the CNS may still be dynamic. Furthermore, the experience at the Irrua Specialist Teaching Hospital, Irrua, Nigeria,<sup>16-18,27</sup> would suggest that the clinical spectrum of CNS involvement in Lassa fever and the effect on outcome may be underestimated, possibly grossly under-reported, and also still dynamic. This might indicate that with advancement in case recognition, diagnostic, and therapeutic techniques, the spectrum of clinical features, especially neurological manifestations might still broaden.

**Table 2: Major viral haemorrhagic fevers: epidemiological characteristics.<sup>1</sup>**

Family	Arenaviridae		Bunyaviridae		Filoviridae		Flaviviridae		
	LF	ArHF	CCHF	RVF	EVD	MHF	DHF	OHF	
Vector/host	<i>Mastomys natalensis</i>	Cricetine rodents	Ticks of the genus Hyalomma	<i>Aedes mcintoshi</i> , <i>Aedes vexans</i> , <i>Culex pipers</i>	Fruit bat	<i>Rousettus aegyptiacus</i>	<i>Aedes aegypti</i>	<i>Dermacentor reticulatus</i>	<i>Aedes aegypti</i> / monkeys
Main mode(s) of transmission	Vector-human; human-human	Aerosolised excreta of vector	Vector-human; contact with infected livestock; nosocomial	Vector-human	Human-human	Human-human	Vector-human	Bite of infected tick; contact with infected animal	Bite of infected mosquito
Geographical location	West Africa	Humid pampas of Argentina	Africa; Middle East; Balkans; Asia	Sub-Saharan Africa; Arabian peninsula	East and Central Africa	East and Central Africa, South Africa	Tropical and subtropical regions of the world	Russia	Tropical and subtropical Africa and South America
Diagnostic tests	RT-PCR		ELISA; viral isolation	ELISA; viral isolation	ELISA; viral isolation; antigen capture; serum neutralising antibody; electron microscopy	ELISA; viral isolation; antigen capture; serum neutralising antibody	RT-PCR; IFA; immunohistochemistry; paired convalescent sera	ELISA	RT-PCR; ELISA
	IFA; ELISA; paired convalescent sera; immunohistochemistry								
Treatment	Supportive		Supportive		Supportive; convalescent serum; experimental drugs and immunoglobulins		Supportive		
	Ribavirin; immune plasma								
Available human vaccine	No	Yes	Yes	No	No	No	No	Yes	

VHF: viral haemorrhagic fever; LF: Lassa fever; ArHF: Argentine haemorrhagic fever; CCHF: Crimean-Congo haemorrhagic fever; RVF: Rift Valley haemorrhagic fever; EVD: Ebola virus disease; MHF: Marburg haemorrhagic fever; DHF: Dengue haemorrhagic fever; OHF: Omsk haemorrhagic fever; YF: yellow fever; RT-PCR: reverse transcription polymerase chain reaction; IFA: immunofluorescence assay; ELISA: enzyme-linked immunosorbent assay.

CNS involvement does not equate to higher mortalities in all cases. There are differences in mortality between different families (e.g. *Arenaviridae* versus *Flaviviridae*) and within family members (e.g. *Flaviviridae*: Omsk haemorrhagic fever versus yellow fever) (Table 2). The reason is probably due partly to the types of associated organ systems involved, and how severely affected the organ is. For example, gastrointestinal symptoms, bleeding, and shock are prominent in Filovirus infection; while hepatic failure is usual in yellow fever. Furthermore, viral load, viral strain, initial dose of inoculum, route of infection, and host factors may play significant roles in determining the severity of infection.

In VHF that cause severe bleeding, the pathogenic mechanism involves abnormalities in haemostasis and microvascular instability leading to shock syndromes in severe cases.<sup>1</sup> The mechanism of CNS disease in VHF is not clear-cut, as not one mechanism fits all VHFs and the spectrum of neurological features associated with them (metabolic, cytopathic, and immune-mediated mechanisms) have been variously postulated with sometimes convincing arguments. Metabolic encephalopathy from multi-organ involvement may explain the CNS disease in many instances. However, clinical and laboratory features indicative of breach of the blood-brain barrier<sup>27,31</sup> and infection of different regions of the grey areas of the brain parenchyma<sup>20,21,25,36,52</sup> would suggest direct effects of the virus. Experimental animal models have lent support to the possible neurotropic effect of some VHF.<sup>24,53</sup> VHF viral particles have been recovered from the CSF<sup>20,25,31</sup> and from brain parenchyma tissues of humans.<sup>54</sup> Furthermore, electroencephalogram and MRI findings have shown evidence of encephalitis in some cases.<sup>20,21,52</sup> Support for an immune-mediated mechanism comes from neurological manifestations occurring during the convalescent or post-infectious periods of infections.<sup>10,15,20,21,29,39</sup>

CNS manifestations usually indicate late stages of the VHF disease with consequent increases in mortality.<sup>17,30</sup> Reported CNS features in VHFs include meningitis, seizures, irritability, tremors, confusion, disorientation, cranial nerve dysfunction, ataxia, neuropsychiatric syndrome, and altered levels of consciousness, including coma.<sup>10,17,20,27,36,38,39,41</sup> These features are due to meningeal irritation from inflammation of the meninges and brain parenchymal injury, alone or in combination.

However, the degree or frequency of CNS involvement differs amongst the various VHF (Table 2). Some VHF viruses have strong predilection for the CNS in the natural course of the disease while others are not as strong.<sup>1</sup> For example, the prevalence of CNS disease in Omsk haemorrhagic fever may be between 30% and 50%<sup>12</sup> and the frequency  $\leq 40.6\%$  in hospitalised Lassa fever patients.<sup>29</sup> Therefore, the incidences of aseptic meningitis and encephalitis among the VHF viruses would be expected to vary. Even though CNS infections are regarded as serious diseases, meningeal involvement alone causing aseptic meningitis may have a good prognosis, for example in Lassa fever.<sup>27</sup> Reported cases of encephalitis without significant involvement of other organ systems are rare; it is therefore difficult to ascertain the impact on outcome when the VHF viruses infect the brain parenchyma alone. However, in general, a clinical diagnosis of encephalitis may be associated with poor prognosis.<sup>17,31,36,39</sup> But the encephalopathy resulting from dehydration, metabolic dysfunction, and electrolyte perturbations due to blood loss, diarrhoea, vomiting, and hepatic and renal dysfunction, which may be present in patients with multi-organ disease, including the CNS, may influence the clinical course and outcome as well. Some clinical features of encephalopathy, such as disorientation, confusion, altered levels of consciousness, and coma, may be indistinguishable from features due to encephalitis, making separation of the contribution of brain injury to disease severity and outcomes in patients with multi-organ disease difficult. Even among the same families of VHF viruses and virus species, there is variation in frequency and severity of CNS disease (Table 2).<sup>1</sup>

Some patients may not have bleeding as a clinical feature, and CNS disease may be the only clinical manifestation of VHF,<sup>10,27,31</sup> which may partly explain the reported low incidence of CNS manifestation in some VHF, because without bleeding patients may not seek medical help, and many clinicians may not suspect VHF.<sup>49</sup>

Effectively addressing these constraints would require regular awareness campaigns and health education targeted at healthcare workers and the communities, and emphasis placed on the fact that bleeding is not always present in VHF. In addition, assistance from, and collaboration with international institutions and agencies that have the expertise in dealing with these diseases is essential in

developing the necessary manpower and infrastructure. Increased participation of governments, especially in providing the political will and enabling financial environment, is desirable.

## CONCLUSION

VHF viruses have varying degrees and spectrums of CNS involvement. In some cases of VHF, CNS features form a great proportion of the clinical

features and contribute significantly to mortality and morbidity. The exact burden of CNS disease on the population in endemic areas is not known. Proper evaluation of patients is hindered by weak health infrastructures in most of the regions where the VHFs are endemic. More resources, human and financial, are needed to aid in the diagnosis, evaluation, and management of patients with CNS disease caused by VHF.

## REFERENCES

- Schlossberg D, "Viral Haemorrhagic fevers", Schlossberg D (ed.), Clinical Infectious Disease (2008) 1<sup>st</sup> edition, New York: Cambridge University Press, pp.1319-32.
- Centers for Disease Control and Prevention. Viral Haemorrhagic Fevers (VHFs). Available at: <https://www.cdc.gov/vhf/virus-families/index.html>. Last accessed: 6 July 2017.
- Bah El et al. Clinical Presentation of Patients with Ebola Virus Disease in Conakry, Guinea. *N Engl J Med*. 2015; 372(1):40-7.
- Goba A et al. An Outbreak of Ebola Virus Disease in the Lassa Fever Zone. *J Infect Dis*. 2016;214(Suppl 3):S110-21.
- Timen A et al. Responses to imported cases of Marburg hemorrhagic fever, the Netherlands. *Emerg Infect Dis*. 2009; 15(8):1171-5.
- Gear JS et al. Outbreak of Marburg virus disease in Johannesburg. *Br Med J*. 1975; 4(5995):489-93.
- Simpson DIH. Viral haemorrhagic fevers of man. *Bull World Health Organ*. 1978;56(6):819-32.
- Peters CJ. "Marburg and Ebola virus hemorrhagic fevers", Mandell GL et al. (eds.), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease (2005) 6th edition, Philadelphia: Elsevier Inc, pp.2057-9.
- Asogun DA et al. Molecular diagnostics for lassa fever at Irrua specialist teaching hospital, Nigeria: lessons learnt from two years of laboratory operation. *PLoS Negl Trop Dis*. 2012;6(9):e1839.
- Maiztegui JI et al. Efficacy of immune plasma in treatment of Argentine Haemorrhagic fever and association between treatment and a late neurological syndrome. *Lancet*. 1979; 314(8154):1216-7.
- Busygin FF. [Omsk hemorrhagic fever-Current status of the problem]. *Vopr Virusol*. 2000;45(3):4-9. (In Russian).
- Ruzek D et al., "Omsk Haemorrhagic Fever Virus", Liu D (ed.), Manual of Security Sensitive Microbes and Toxins (2014), CRC Press, pp.193-200.
- Weiss KE. Rift valley fever-a review. *Bull Epizoot Dis Afr*. 1957;5:431-58.
- Borio L et al. Hemorrhagic fever viruses as biological weapons: medical and health management. *JAMA*. 2002; 287(18):2391-405.
- Cummins D et al. Acute sensorineural hearing loss in Lassa fever. *JAMA*. 1990;264(16):2093-6.
- Okokhere P et al. The Effect Of Malaria On The Outcome Of Lassa Fever. *Int J Infect Dis*. 2010;14 S1:72.003;e333.
- Okokhere PO et al. Central nervous manifestation of Lassa fever in Nigeria and the effect on mortality. *J Neurol Sci*. 2013;333(Suppl 1):e604.
- Okokhere PO et al. Sensorineural hearing loss in Lassa fever: two case reports. *J Med Case Rep*. 2009;3:36.
- Puccioni-Sohler M et al. Neurological complication in Dengue infection: a review of clinical practice. *Arq Neuropsiquiatr*. 2013;71(9B):667-71.
- Jacobs M et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet*. 2016;388(10043):498-503.
- Howlett P et al. Ebola Virus Disease Complicated by Late-onset Encephalitis, Sierra Leone. *Emerg Infect Dis*. 2016; 22(1):150-2.
- World Health Organization (WHO). Ebola virus disease. Available at: <http://www.who.int/mediacentre/factsheets/fs103/en/>. Last accessed: 6 July 2017.
- World Health Organization (WHO). WHO: Ebola response roadmap update. Available at: [http://apps.who.int/iris/bitstream/10665/136645/1/roadmapupdate17Oct14-\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/136645/1/roadmapupdate17Oct14-_eng.pdf?ua=1). Last accessed: 6 July 2017.
- Centre for Disease Control and Prevention. Ebola haemorrhagic fever. Available at: <https://www.cdc.gov/vhf/ebola/>. Last accessed: 6 July 2017.
- Geisbert TW et al. Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques: evidence that dendritic cells are early and sustained targets of infection. *Am J Pathol*. 2003;163(6): 2347-70.
- de Greslan T et al. Ebola-virus related encephalitis. *Clin Infect Dis*. 2016;63(8):1076-8.
- Okokhere P O et al. Aseptic Meningitis Caused by Lassa Virus: Case Series Report. *Case Rep Neurol Med*. 2016;2016:1978461.
- Ibekwe TS et al. Early-onset sensorineural hearing loss in Lassa fever. *Eur Arch Otorhinolaryngol*. 2011; 268(2):197-201.
- Solbrig MV, McCormick JB. Lassa fever: central nervous system manifestations. *J Trop Geogr Neurol*. 1991;1:23-30.
- Cumming D et al. Lassa fever encephalopathy: clinical and laboratory findings. *J Trop Med Hyg*. 1992;95(3): 197-201.
- Günther S et al. Lassa Fever Encephalopathy: Lassa virus in Cerebrospinal fluid but not in serum. *J Infect Dis*. 2001;184(3):345-9.
- Liao BS et al. Audiometric comparison of Lassa fever hearing loss and idiopathic sudden hearing loss Evidence for viral cause. *Otolaryngol Head Neck Surg*. 1992;106(3):226-9.
- Peter S et al. Isolated Bell's palsy - an unusual presentation of dengue infection. *Asian Pac J Trop Med*. 2013;6(1):82-4.
- Verma R et al. Neurological complications of Dengue fever: Experience from a tertiary center of north India. *Ann India Acad Neurol*. 2011;14(4):272-8.
- Misra UK et al. Neurological manifestations of dengue virus infection. *J Neurol Sci*. 2006;244(1-2):117-22.
- van Velden DJ et al. Rift valley fever affecting humans in South Africa: A clinicopathological study. *S Afr Med J*. 1977;51(24):867-71.
- Alrajhi AA et al. Rift valley fever encephalitis. *Emerg Infect Dis*. 2004; 10(3):554-5.

38. Al-Tikriti SK et al. Congo/Crimean haemorrhagic fever in Iraq. *Bull World Health Organ.* 1981;59(1):85-90.
39. Biguard C et al. [Neurological study of 120 cases of Argentine hemorrhagic fever]. *Prensa Med Argent.* 1969;56(14):605-14. (In Spanish).
40. Carballal G et al. Epidemiology of argentine hemorrhagic fever. *Eur J Epidemiol.* 1988;4(2):259-74.
41. Elton NW et al. Clinical pathology of yellow fever. *Am J Clin Pathol.* 1955; 25(2):135-46.
42. Roos KL, Tyler KL. "Meningitis, Encephalitis, Brain Abscess, and Empyema", Fauci AS et al. (eds.), *Harrison's Principles of Internal Medicine* (2008) 18<sup>th</sup> edition, New York: McGraw-Hill Companies, pp.2621-40.
43. McCormick JB et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med.* 1986;314(1):20-6.
44. Chevallier MS et al. Ebola virus disease cluster in the United States-Dallas County, Texas, 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63(46):1087-8. Erratum in: *MMWR Morb Mortal Wkly Rep.* 2014;63(48):1139.
45. Bowen GS et al. Lassa fever in Onitsha, East Central State, Nigeria, in 1974. *Bull World Health Organ.* 1975;52(4-6):599-604.
46. World Health Organization (WHO). Interim Infection prevention and control guidance for care of patients with suspected or confirmed Filovirus Haemorrhagic Fever in in health-care settings, with focus on Ebola. Available at: [http://apps.who.int/iris/bitstream/10665/130596/1/WHO\\_HIS\\_SDS\\_2014.4\\_eng.pdf?ua=1&ua=1&ua=1](http://apps.who.int/iris/bitstream/10665/130596/1/WHO_HIS_SDS_2014.4_eng.pdf?ua=1&ua=1&ua=1). Last accessed: 6 July 2017.
47. Bausch DG et al. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa fever. *Clin Infect Dis.* 2010;51(12):1435-41.
48. Kyei NNA et al. Imported Lassa fever: a report of 2 cases in Ghana. *BMC Infect Dis.* 2015;15:217.
49. Dzotsi EK et al. First Cases of Lassa fever in Ghana. *Ghana Med J.* 2012; 46(3):166-70.
50. Fischer-Hoch SP et al. Review of cases of nosocomial Lassa fever In Nigeria: The high price of poor medical practice. *BMJ.* 1995;311:857-9.
51. Shaffer JG et al. Lassa fever in post-conflict Sierra Leone. *PLoS Negl Trop Dis.* 2014;8(3):e2748.
52. Wasay M et al. Encephalitis and myelitis associated with Dengue viral infection: clinical and neuroimaging features. *Clin Neurol Neurosurg.* 2008;110(6):635-40.
53. Yun NE et al. Animal model of sensorineural hearing loss associated with Lassa virus infection. *J Virol.* 2015; 90(6):2920-7.
54. Ramos C et al. Dengue virus in the brain of a fatal case of Dengue hemorrhagic fever. *J Neurovirol.* 1998;4(4):465-8.

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