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Ebola: A review and focus on neurologic manifestations

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ABSTRACT

Ebolavirus disease (EVD) is a severe, highly contagious, and often fatal systemic disease in human and non-human primates. Zoonotic and human-to-human transmission have been well documented. *Ebolaviruses* are endemic to Equatorial and West Africa and there have been over 20 outbreaks in sub-Saharan Africa since 1976. The largest known outbreak of EVD occurred between 2013 and 2016 across several West African countries. It resulted in 28,646 suspected and confirmed cases and 11,323 deaths. There are 5 species within the genus *Ebolavirus* with 4 of them being clinically significant. In patients with EVD, neurologic manifestations range from mild symptoms such as confusion to severe neurologic diseases such as meningitis and encephalitis. Altered mental status, from mild confusion to delirium with hallucinations, may also occur. Rare neuropsychiatric manifestations of EVD include psychological or cognitive symptoms, including short-term memory loss, insomnia, and depression or anxiety. Although Ebolavirus RNA has been detected in cerebrospinal fluid, the body of knowledge around the pathogenic mechanisms of neurological disease is not yet fully understood. Studies are needed to understand the acute and chronic neuronal pathologic as well as biochemical cerebrospinal fluid changes in *Ebolavirus* infection.

1. Introduction

Ebolavirus disease (EVD) is a viral hemorrhagic fever caused by viruses of the genus *Ebolavirus*. It is a severe, highly contagious, and often fatal systemic disease in human and non-human primates. In the strict sense, EVD refers to a disease caused by the specie, *Zaire Ebolavirus*, however, for the purpose of this review we will refer to it as a clinical disease caused by the species in the genus *Ebolavirus*. EVD was first identified in Yambuku village about 60km from the Ebola river in Zaire (now known as the Democratic Republic of Congo – DRC) in 1976 [1]. This first known outbreak of EVD was caused by the specie *Zaire Ebolavirus*. A simultaneous outbreak caused by a closely related, less fatal specie, *Sudan Ebolavirus* was evolving in South Sudan around the same time [2,3]. In the following decades, 4 species of Ebolavirus causing EVD were identified in outbreaks in mostly rural parts of DRC, South Sudan and Uganda [1]. The largest known outbreak of EVD occurred between 2013 and 2016, originating in Guinea, West Africa, spreading to neighboring Liberia and Sierra Leone, across several other West African countries and eventually to Europe and the United States of America [4]. It resulted in 28,646 suspected and confirmed cases and 11,323 deaths [4].

The magnitude and prolonged duration of that EVD epidemic provided opportunities to generate much of the current knowledge about the pathogenesis and clinical course of the disease [5].

Ebolavirus is known to be zoonotic in transmission with human-to-human transmission through infected body fluids and corpses are well established. The natural reservoir host is widely believed to be the fruit bat of the *Pteropdidae* family [6,7].

2. Epidemiology

Ebolaviruses are endemic to Equatorial and West Africa and there have been over 20 outbreaks in sub-Saharan Africa since 1976, mostly affecting DRC, Sudan, Congo, Uganda and Gabon [8,9]. The *Zaire Ebolavirus* and the *Sudan Ebolavirus* are responsible for most of these outbreaks while the *Bundibugyo Ebolavirus* is only known to have caused a few smaller outbreaks [10]. Initially, the outbreaks mostly occurred in isolated rural areas without significant spread to major urban areas. The

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West African EVD outbreak of 2013–2016 was different from this in that while it is believed to have emerged from a rural part of Guinea, it spread quickly to major urban areas in Guinea and neighboring countries [10]. The spread of EVD was fueled by densely populated urban areas, highly mobile populations, porous borders and poor sanitary conditions in the sub-region [10]. It is also believed that traditional or cultural practices such as corpse preparation by relatives for burial and a mistrust of local healthcare and other authorities contributed to the spread of EVD [11].

3. Classification

Filoviruses of human importance have recently been sub-classified into the two genera *Ebolavirus* and *Marburgvirus* (WHO ICD-11 2018) [12]. The family *filoviridae* within the order *Mononegavirales* are single strand, negative sense viruses [5]. There are 5 species within the genus *Ebolavirus*, with 4 of them being clinically significant. They are: *Bundibugyo ebolavirus*, *Sudan ebolavirus*, *Taï Forest*Ebolavirus and *Zaire* Ebolavirus. *Reston* Ebolavirus is not known to cause significant disease in humans [13] (Table 1).

4. Laboratory diagnosis

In the past, diagnosis of EVD was made by viral isolation with cell culture. However, this has been replaced by molecular diagnostics in more recent times, especially since the 2013–2016 West African outbreak. The mainstay of EVD diagnosis is currently real-time reverse transcription polymerase chain reaction (RT-PCR) to detect viral RNA which is usually detectable in blood by the time of presentation to a healthcare facility or a few days after the onset of symptoms [17]. It is important that the tests are conducted in individuals to whom an appropriate case definition has been applied and reasonably fulfilled. A negative EVD test in a symptomatic patient in the early stages or soon after the onset of symptoms, with epidemiologic linkage especially within the context of an outbreak should be repeated serially over the next 2–3 days [5].

Among EVD survivors, viral RNA may remain detectable in blood for up to 21 days [5], while IgM and IgG become detectable around days 5–10 and 7–14 respectively [18]. IgM has been documented to persist for 1–6 months [18]. Expectedly, IgG persists for a longer period of time; a study following up EVD survivors for 2 years documented persistence of IgG at 2 years; however, it is not known whether IgG continues to be detectable after 2 years among EVD survivors [19]. At least some antibody response should be detected by the third week in most patients. However, non-survivors may not develop IgM and IgG antibodies before death [19,20]. This is either an indication of early death before antibody production occurred or death possibly related to defective humoral immunity. Therefore, using serologies alone is not adequate for diagnosis in symptomatic patients.

Individuals with mild or no symptoms may have viral loads below the limit of detection in blood by Polymerase Chain Reaction (PCR). In these individuals, antibodies may be useful for making a diagnosis. It should be noted that in these asymptomatic patients, antibodies develop later than in symptomatic viremic patient (as late as 3 weeks) [21,22]. *Ebolavirus* can be detected in body fluids other than blood such as breast milk, seminal fluid, saliva, sweat and may persist in these fluids long after viremia has resolved [23–25]. In terms of neurological imaging, there are no known classic or pathognomonic features that have been found to typify EVD with neurological involvement.

Table 1
Classification, taxonomy and other features.

Species	Name of virus	Location of initial outbreak, year	Case fatality rate	Comments
Zaire ebolavirus	Ebola virus (EBOV)	Democratic Republic of Congo, 1976	60–80% [2,14]	Most widely studied, its Makona variant was responsible the West Africa outbreak of 2013–2016 [11]
Sudan ebolavirus	Sudan virus (SUDV)	South Sudan, 1976	50% [3,15]	
Reston ebolavirus	Reston virus (RESTV)	Philippines, 1989	_	Does not appear to cause human disease
Taï Forest ebolavirus	Taï Forest virus (TAFV)	Cote d'Ivoire, 1994	_	Only one known case to date
Bundibugyo ebolavirus	Bundibugyo virus (BDBV)	Uganda, 2007	25–32% [15,16]	

5. Clinical features

5.1. Neurological manifestation of Ebolavirus disease

The neurologic manifestations of EVD may be seen in the acute stage or later on in the course of disease. Long-term neurologic sequelae have also been described. Some symptoms may be seen at any stage of EVD; hence it is difficult to distinctly classify symptoms or signs as early or late. It is however notable that in the acute phase, patients with EVD tend not to have severe neurologic manifestations [26]. Some neurological features have been reported in several studies while some are yet to be well reported and fully characterized (Table 2). Features well reported are headaches [26,28–30], hearing impairment [26,27,31,32] and visual disturbances [27–32]. Overall, CNS symptoms have been reported as rare in studies involving both children and adults [26,33].

A non-specific headache is the most commonly described acute neurologic symptom of EVD [26]. A World Health Organization report chronicling the first 9 months of the West Africa outbreak in 4 of the countries affected in West Africa reported that 53% of patients reported headache [34]. The commonest neurological feature of EVD reported among survivors in Sierra Leone was also headache [29]. Alterations in sensorium may occur, ranging from mild confusion to delirium and even coma in cases of severe EVD [28]. These may occur as a result of virus-related encephalitis, electrolyte derangements caused by large volume diarrhea and vomiting or sepsis related cerebral hypoperfusion [34].

Severe symptoms such as encephalitis are rare and occur much later in the course of disease [26]. Meningitis and encephalitis have been reported in recent EVD outbreaks, as well as in prior outbreaks, although the incidence is not well documented [31,32,35]. A patient managed at the National Institutes of Health (NIH) USA developed meningoencephalitis with classic features after the first week of illness [26]. Late-onset encephalitis, has been reported in one case after 64 days of EVD [35]. Another patient, a Scottish nurse who had been involved in the response to the West African outbreak, developed features of acute meningitis 9 months after she was treated for EVD [36]. She also developed cranial neuropathies and radiculopathy. As of thetime of initial treatment and discharge, the Ebolavirus RNA was undetectable in her peripheral blood. It was however detected in her cerebrospinal fluid (CSF) and again in peripheral blood (at higher levels in her CSF than blood) during her relapse.

In the Prevail III study of EVD sequelae in Liberia, the authors found that the most common abnormalities on neurologic examination among EVD survivors and controls were abnormal reflexes (1.4% and 0.7%, respectively), tremor (0.9% and 0.2%), gait or balance abnormalities (0.7% and 0.9%), speech abnormalities (0.7% and 0.2%), and cranial nerve abnormalities (0.7% and 0.1%) [37]. Psychological or cognitive symptoms of EVD (though rare) have been reported, these include short-term memory loss, insomnia, and depression or anxiety [38]. An EVD patient who had evidence of previous hemorrhagic encephalitis on a Magnetic Resonance Image (MRI), later had a grand mal seizure, presumably from epileptogenic scar tissue [39].

Other rare neurological manifestations include difficulty

Table 2
Neurological manifestations of *Ebolavirus* disease.

Author	Type of studies	Year, country of outbreak onset	Maximum duration of follow-up	Number of survivors/ controls studied/followed	Summary of findings
Billioux et al. [26]	Review of Neurological Complications of Ebola Virus Infection	2016	–	–	A number of neurologic complications such as seizures, memory loss, headaches, cranial nerve abnormalities, and tremors can occur after EVD. Ebola viruses may also persist in some immunologically privileged sites, including the central nervous system, and can rarely lead to disease relapse.
Scott et al. [27]	Cross-sectional survey	2016, Sierra Leone	After discharge at their initial follow-up appointment within 3 weeks after their second negative PCR result	44 survivors	Survivors reported musculoskeletal pain (70%), headache (48%), and ocular problems (14%)
West et al. [28]	Review	2014			Headache was the only neurological manifestation
Mohammed et al. [29]	Observational	2015, Sierra Leone	median time from EVD discharge to attendance was 261 days (range 4–504 days).	115	The most commonly reported signs and symptoms among the 621 attendances were headache (63.1%), fever (61.7%), and myalgia (43.3%).
Wilson et al. [30]	Cross sectional	2016	3–6 months	300	Eye problems, headache, sleep disorders, and unusual tiredness
Bwaka et al. [31]	Observational	1995, Democratic Republic of the Congo	2 months	19	Arthralgia (37%), conjunctivitis (11%), hearing loss or tinnitus (11%), uveitis (5%), unilateral vision loss (5%), suppurative parotitis (5%), unilateral orchitis (5%), pericarditis (5%), weight loss, asthenia, frequent intercurrent infections (malaria and urinary tract)
Sagui et al. [32]	Case report	2015	5 days of infection	1	The patient showed signs of encephalopathy 7 days after the onset of symptoms
Howlett et al. [35]	Case report	2014, Sierra Leone	64 days	1	Late-onset encephalitis, CT scan showed cerebral atrophy without hydrocephalus
Sneller et al. [37]	Prospective cohort	2019, Sierra Leone	12 months	A total of 966 EBOV antibody-positive survivors and 2350 antibody-negative close contacts (controls) were enrolled	six symptoms were reported significantly more often among survivors than among controls: urinary frequency (14.7% vs. 3.4%), headache (47.6% vs. 35.6%), fatigue (18.4% vs. 6.3%), muscle pain (23.1% vs. 10.1%), memory loss (29.2% vs. 4.8%), and joint pain (47.5% vs. 17.5%). On examination, more survivors than controls had abnormal abdominal, chest, neurologic, and musculoskeletal findings and uveitis. Other than uveitis (prevalence at enrollment, 26.4% vs. 12.1%; at year 1, 33.3% vs. 15.4%), the prevalence of these conditions declined during follow up in both groups.
Epstein et al. [38]	Follow up	2015, United States	5 months (range, 4–7)	8	3 (38%) developed Peripheral paraesthesia or dysesthesia
Vetter et al. [39]	Review	2016			True viral encephalitis, or secondary post-viral complications such as acute disseminated encephalomyelitis. Encephalopathy and cerebrovascular accidents with residual neurological deficits have been described in Ebola disease. Transient paroxysmal fevers suspected to be of CNS origin. Tinnitus, hearing loss, altered sense of smell and taste and neuropathy.
Chertow et al. [40]	Perspective	August 23 and October 4, 2014, Liberia		Cared for more than 700 patients with Ebola disease	Meningoencephalitis is a presumptive diagnosis based on the clinical features of unconsciousness and stiff neck

concentrating, mood changes, peripheral paresthesia or dysethesia, dizziness, and profound tiredness [26,27,30,31]. During acute disease, seizures have also been reported, although these are not well characterized [40]. Seizure has also been reported in a case of relapse with meningoencephalitis [36]. Neurological manifestations have been linked with mortality. A study in West Africa showed individuals with respiratory, neurological, or hemorrhagic symptoms have a higher risk of death [28].

In a case series of EVD survivors in Sierra Leone, acute neurologic presentations of these survivors at the time of Ebola diagnosis were seizures and altered level of consciousness [41]. Undifferentiated and migraine headaches were the most common long term neurologic features. Other neurologic presentations of EVD were peripheral sensory neuropathy, peripheral nerve lesions, and stroke. On CT brain imaging, abnormal findings were reported in 7 out of the 17 survivors. Of these, 3 had brain atrophy, 2 calcifications, and 2 had evidence of stroke. Sleep difficulties and anxiety and depressive symptoms were common psychiatric abnormalities documented from these EVD survivors [41].

MRI findings have not been widely reported for obvious reasons. A 34-year-old man with severe EVD and multi-organ failure was noted during the convalescent period (day 33 after presentation) to have MRI findings consistent with micro-vascular occlusion and ischemia, no signs of hemorrhage were seen [42]. These vascular findings are not surprising as vascular endothelial infection is one of the known pathogenic mechanisms of EVD. CSF examination in this patient was done 7 months after presentation and revealed no *Ebolavirus* RNA. The previously mentioned Scottish nurse had patchy leptomeningeal enhancement on contrast-enhanced MRI of the brain, mainly involving the brainstem,

cranial nerves, cauda equina, and conus medullaris, with abnormal left cerebellar enhancement done on day 31 of relapse with meningoencephalitis [36]. CSF examination in this patient revealed the presence of white blood cells though not quantified for biosafety reasons [36].

Adequate study and documentation of the neurological signs of EVD have been hampered by the challenges of conducting a detailed neurological examination while wearing the requisite protective equipment. Strict isolation in containment areas also limits their access to neuroimaging. In addition, the relatively low resource setting in which these patients have been nursed are another reason for limitation in terms of access to neuro imaging and other diagnostic facilities. Nevertheless, there have been some patients managed in these and resource rich settings who have contributed significantly to what is known about the disease. In addition, the >17,000 survivors of the 2013–2016 EVD pandemic have provided much opportunity for the study of neurological complications and post-acute sequelae.

6. Treatment of *Ebolavirus* disease

Therapeutic interventions are needed to treat acute and long-standing neurologic and other manifestations of EVD. Several therapeutic regimens have been tried in the management of EVD albeit with little success with some putative regimen. Remdesivir is a broad-spectrum antiviral regimen initially developed for the treatment of EVD. In randomized clinical trials, Remdesivir's efficacy is below the therapeutic end points despites its good performance in the pre-clinical studies [43]. The PREVAIL II study reported lower mortality in the group of patients who used standard treatment regimen with ZMapp than ZMapp alone. However, a randomized control trial in the Democratic Republic of Congo reported lower efficacy of ZMapp compared to the monoclonal antibodies MAb114 and REGN-EB3 [44].

7. Transmission

7.1. Zoonotic transmission of Ebolavirus

Bats of various species are believed to be the vectors for zoonotic transmission of *Ebolavirus* in Africa [6,45,46], although evidence indicates additional zoonotic reservoir hosts in the maintenance of the *Ebolavirus* in the epidemiologic transmission cycle [8]. Fedewa and colleagues successfully demonstrated the non-cytopathic replication of *Ebolavirus* in python and boa constrictor cells lines, suggesting that snakes may be a natural reservoir for the virus [47,48].

Serologic evidence of *Ebolavirus* has been demonstrated in fruits bats isolated from Ghana: African straw collared fruit bat (*Eidolon helvum*), and the Gambian *epauletted* fruit bat (*Epomophorus gambianus*) [4]. Ecologic investigation into the origin of the 2013–2016 West African *EVD* outbreak can be traced to zoonotic transmission as the index case may have been infected by exposure to *Mops condylurus*, an insectivorous free-tail bat [49]. A 2018 routine zoonotic surveillance of zoonotic viruses in Sierra Leone detected a new *Ebolavirus* specie called the *Bombali ebolavirus* in the free-tail bats (Species: *Mops condylurus* and *Chaerephonpumilus*) [50]. Unfortunately, the same species of *Ebolavirus* was also discovered in neighboring Guinea [51], indicating a sub-regional spread of emerging strains of *Ebolavirus* in bat reservoirs.

The clear demonstration of zoonotic transmission of *Ebolavirus* and other *filoviruses* calls for a more robust approach to improving the surveillance for zoonotic infections in the West African sub-region and indeed throughout Sub-Saharan Africa. Community-based infection control interventions targeting the reduction of interaction between the wildlife and human population are needed for the prevention of potential outbreaks of *Ebolavirus* and other zoonotic infections.

7.2. Nosocomial and non-zoonotic community-based EbolavirusE /transmission

Secondary EVD transmission in health facilities is a major public health concern as it can amplify community spread of the infection and perpetuate an EVD outbreak [52]. Direct exposure to body secretions of an infected person is a well-known means of transmission of *Ebolavirus* in both community and hospital settings [52]. Although controversial, aerosol transmission especially with aerosol generating procedures, has also been implicated in the spread of the *Ebolavirus* in healthcare settings [9]. The impact of nosocomial *Ebolavirus* transmission on the health system is enormous. Out of the 3854 laboratory-confirmed cases of EVD reported in Sierra Leone by October 2014, 199(5.2%) were healthcare workers, giving a cumulative confirmed Ebola incidence of 8.285 per 100,000 among healthcare workers [53,54].

Resource constraints and lack of policies on infection prevention and control practices contributed to the spread and significant morbidity and mortality of the 2014–2016 West African EVD epidemics. Improved access to personal protective equipment and other infection control resources are among the strategies for reducing nosocomial transmission [10,55]. Generally, however, the availability of effective vaccines could be a major preventive strategy against the EVD. Fortunately, there has been a significant progress in the development of vaccine against the Ebola virus. In the ring vaccine trial in Guinea, the rVSV-ZEBOV demonstrated substantial protection against the *Ebolavirus* [56]. Traditional practices such as traditional care of sick people and washing of dead bodies at home were also a major driver of transmission of *Ebolavirus* during the 2014–2016 EVD epidemic in West Africa and such practices encouraged a community accentuation of the epidemic [11].

7.3. Other means of Ebolavirus transmission

Sexual intercourse is another means of *Ebolavirus* transmission due to the persistence of the virus in the seminal or vaginal secretions [57]. Although sexual transmission is rare, the World Health Organization issued out rapid advice on sexual transmission of EVD during the 2014–2016 West African *Ebolavirus* outbreak, encouraging male survivors to apply preventive measures until a negative *Ebolavirus* reverse transcriptase RNA was obtained in their seminal fluid [58]. In spite of the detection of *Ebolavirus* RNA by RT-PCR in the female genital secretions of a woman 33 days after symptom onset, there was no evidence of female-to-male transmission [59]. Mathematical modelling, however, revealed a significant contribution of male-to-female sexual transmission of the *Ebolavirus* during the 2014–2016 epidemic in West Africa [60].

Detectable levels of *Ebolavirus* RNA can also occur in breast milk and cerebrospinal fluid [24,60]. Despite the lack of definitive evidence on the transmission of *Ebolavirus* through breastfeeding, precautionary measures are needed when the *Ebolavirus* RNA is detected in breast milk [59].

8. Pathogenesis of *Ebolavirus*

Viral pathogenesis is the mechanism by which a viral infection results in a disease. The initial phase requires attachment of the virus to the host cell surface. Subsequent events include entry and replication within cells of target organ. Cytokines and toxin production and direct cytopathic effect of the virus leads to tissue or organ damage [61].

9. Cells and cellular changes

After transmission, the *Ebolavirus* uses its glycosylated surface glycoprotein to enter the host cellular structure through an interaction with various surface molecules including heparan sulfate [62,63]. Although the *Ebolavirus* can infect a wide variety of cells including the immune cells (dendritic, monocytes), neurons, endothelial cells,

fibroblasts, hepatocytes, and adrenal cells, it exhibits surface tropism as it enters the host cell through its basolateral surface [64]. Upon entry into the cell through macropinocytosis [65], the virus binds to its endosomal receptor referred to as the cholesterol transporter Niemann-Pick C1 and cause cellular changes [66].

Based on an animal model of pathogenesis of *Ebolavirus*, alveolar macrophages and dendritic cells support the in vivo replication of *Ebolavirus* in the subcellular structures [67,68].

10. Cytokine and inflammatory response

Ebolavirus causes acute febrile illness with significant mortality. Suppression of both the innate and adaptive immune response contributes to the complex series of events that result in this high mortality [69]. The virus typically infects and kills cells resulting in various pathogenic changes including systemic inflammatory response syndrome and disseminated intravascular coagulopathy [69]. Several inflammatory markers mediate the inflammatory changes. Fatal human *Ebolavirus* infections are associated with high levels of TNF-α, and IFN-γ (an inflammatory cytokine implicated as a potential mediator of the shock seen in fatal cases of EVD). Levels of inflammatory mediators including IL-4, IL-2, macrophage inflammatory protein (MIP)-1, and granulocyte-macrophage colony-stimulating factor are raised in patients with EVD [69]. Similarly, a higher level of a chemotactic factor (the RANTE molecule) for eosinophils, lymphocytes, and monocytes has been demonstrated in severe EVD [26].

11. Neuropathologic changes in *Ebolavirus* disease

The central nervous system is one of the major body systems affected by the cellular and cytokine changes that occur in EVD, resulting in various acute neurologic manifestations such as headache, seizure, insomnia, meningoencephalitis, and coma [26]. Although the *Ebolavirus* initially replicates in the liver and spleen as primary target organs, it can hematogenously and lymphogenously disseminate to the central nervous system [70]. However, due to biosafety reasons, there is paucity of information on post-mortem pathologic changes of *Ebolavirus* infection on the brain and spinal cord [26]. Animal model studies with experimentally infected *Zaire Ebolavirus* revealed the presence of the viral antigen in nervous and ocular tissues [72]. Scattered microglial nodules and meningoencephalitis, as well as retinal and corneal inflammatory changes, were observed in these animals [71]. Molecular characterization of CSF in non-human primates revealed a high load of *Ebolavirus* RNA particles that were comparable to the serum RNA levels [72]. In a case report of a 21-year-old man with severe *Ebolavirus* infection, a high level of the viral genetic material was detected in the CSF, indicating remarkable neurologic involvement in this and likely other patients with *Ebolavirus*-related encephalopathy [32].

12. Conclusion

Ebolaviruses remain a clear and present threat to rural and urban populations in sub-Saharan Africa and by extension, the world. While the body of knowledge around the pathogenic mechanisms of neurological disease is growing, they are not fully understood. Consequently, the resulting acute neurologic disease states cannot be precisely targeted with therapeutics and the chronic sequelae are difficult to predict. Therefore, further studies are needed to understand the acute and chronic neuronal pathologic as well as biochemical CSF changes in *Ebolavirus* infection.

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