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An update on ocular complications of Ebola virus disease

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Abstract

Purpose of review—This review provides a summary of our current understanding of the ophthalmic manifestations of Ebola virus disease (EVD), pathogenesis, treatment options and directions for future study. The individual, public health and global health implications of eye disease in EVD survivors are discussed.

Recent findings—The West Africa EVD outbreak was of unprecedented magnitude, leading to the largest survivor cohort since the first documented EVD outbreak in 1976. Because of the magnitude of the recent outbreak, thousands of survivors are at-risk of systemic and ophthalmic sequelae termed the ‘post Ebola virus disease syndrome’. Uveitis is the most common finding during EVD convalescence and may lead to severe vision impairment or blindness in 40% of affected individuals. Ocular complications leading to vision loss include cataract, retinal scarring, optic neuropathy, hypotony and phthisis bulbi. The pathogenesis of eye disease in EVD survivors likely involves Ebola virus persistence, severe inflammation and tissue edema, which present as acute, rapidly progressive disease or chronic, smoldering disease. Further studies into disease pathogenesis including mechanisms of viral persistence may provide guidance into therapies for uveitis secondary to EVD.

Summary—Uveitis is the most common ophthalmic finding in EVD survivors and can lead to vision loss. Further studies into the clinical manifestations and mechanisms of disease are needed to improve therapies for EVD survivors who often have limited access to ophthalmic medical and surgical care.

Keywords

Ebola virus persistence; Ebola virus; uveitis

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The Ebola virus disease (EVD) outbreak of 2013–2016 in West Africa is the largest in history with 28 600 cases leading to approximately 11 300 deaths internationally, particularly within the highest transmission countries of Sierra Leone, Liberia and Guinea [1]. The high viremia and virus shedding in bodily fluids contributed to the infectivity of the virus which led to human-to human transmission and propagation of the epidemic. The outbreak resulted in an estimated 17 000 survivors in West Africa.

Although the West African outbreak was formally declared over in the spring of 2016, Zaire Ebolavirus (EBOV) continues to remain a global health threat with the potential to cause clinical disease in sporadic outbreaks. Specifically, in the Democratic Republic of Congo (DRC), there were eight cases and four deaths attributed to EBOV in May 2017 [2].

Prior to these two recent outbreaks, there were 29 isolated outbreaks that began in 1976, with fewer cases largely because of their rural location away from more densely populated urban centers [3,4]. Because of the sheer volume of cases in the West African epidemic, we are learning more about the sequelae experienced by EVD survivors. An entity has surfaced termed the ‘post-Ebola virus disease syndrome (PEVDS)’. Clinical symptoms include but are not limited to ocular disease, arthritis, hearing loss, abdominal pain and neuropsychiatric disorders as well as viral persistence in immune-privileged organs [5,6]. These findings present additional stresses and challenges to communities that have already been devastated by loss of life, community and infrastructure.

Within the context of PEVDS, uveitis is the most common ocular complication, occurring in approximately 13–34% of survivors in West Africa. Herein, we review the literature describing the ocular complications that have emerged since this unprecedented outbreak in West Africa. These findings have introduced further clinical and scientific questions pertinent to ophthalmologists, infectious disease and public health specialists.

CLINICAL FEATURE OF ACUTE EBOLAVIRUS INFECTION

Background

EBOV is a member of the Filoviridae family (Ebola and Marburg virus) and is an enveloped, filamentous, nonsegmented single stranded RNA-virus. There are five different EBOV species that include Zaire, Sudan, Taï Forest, Reston and Bundibugyo. The Reston EBOV species is lethal to nonhuman primates but does not cause human fatalities. The Zaire EBOV species was responsible for the West Africa epidemic and historically has had the highest case fatality rate. EBOV manifests clinically as a hemorrhagic fever [3,6].

Clinical disease

The incubation period for EBOV is 2–21 days. Initial symptoms include a flu-like illness with fever, headache, malaise and diarrhea. Animal-to-human transmission may occur via direct contact or consumption of animal reservoirs (chimpanzees, gorillas, fruit bats and duikers). Exposure to bodily fluids such as blood, saliva, sweat, urine, breast milk and feces

with mucosal surfaces, open wounds or parenterally may lead to human-to-human transmission [7].

During the initial infection, macrophages and dendritic cells are infected with EBOV. As the virus begins to circulate through the body, other cells are infected including fibroblasts, endothelial cells, hepatocytes, adrenal cortical cells and epithelial cells. The EBOV suppresses dendritic cell activation which in turn decreases cytokine release and T-cell activation. The opposite is occurring in the macrophages with activation and release of cytokines leading to a 'cytokine storm'. In addition, EBOV can downregulate the body's production of interferons, which is a key component of the innate immune viral response. The combination of these responses/derangements leads to increased vascular permeability, hypovolemic shock, multisystem failure, disseminated intravascular coagulation, diffuse hemorrhage, maculopapular rash and ultimately death in many cases.

Laboratory abnormalities can accompany the systemic infection including lymphopenia, transaminitis, increased clotting times, thrombocytopenia, electrolyte abnormalities and elevated creatinine [3,7].

Diagnosis

Laboratory specimens of suspected EVD require a Biosafety Level 4 laboratory for testing. EBOV infection is detected by reverse transcription polymerase chain reaction (RT-PCR) techniques. Other methods include the detection of immunoglobulin M (IgM) and G (IgG) antibodies, and/or recognition of specific EBOV antigens by antigen detection tests.

POST EBOLA VIRUS DISEASE SYNDROME

Systemic disease

Survivors of EVD may complain of fatigue, vision loss, hearing loss, headaches, memory loss, sleep disorders, mood disturbances, abdominal pain, amenorrhea, miscarriages, enthesitis and arthralgias [5,6]. Some of these clinical symptoms and signs have been noted historically after EBOV, Sudan Ebolavirus or Bundibugyo Ebolavirus infections, and described up to 2 years after acute disease [8]. However, these were often self-reported and not been well characterized. Efforts to characterize the clinical syndromes, epidemiology and risk factors, prevention and treatment needs and the underlying pathogenesis are ongoing.

Although the exact pathogenesis of the PEVDS is unclear, potential hypotheses include elevated inflammatory cytokines, molecular mimicry, direct damage from viral infection and viral persistence in immune-privileged sites. These complications highlight the need for ongoing care even after patients have survived the acute illness. In addition, this may ultimately impact function in the workplace, which may have long-term economic implications [6,9,10].

Ocular disease

Within this context, ophthalmic complications remain at the forefront of EVD survivor care because of their prevalence and the profound impact on activities of daily living and quality-

of-life. Uveitis, the most common ocular finding, commonly presents with eye pain, redness and photophobia and may lead to acute or chronic vision loss; the combination of debilitating symptoms and vision impairment makes addressing these aspects of eye disease a crucial aspect of EVD survivor care.

Retrospective series from prior Ebola virus disease outbreaks

During acute EVD, conjunctival injection has been reported in 48–58% of patients in previous outbreaks. In one cohort, bilateral injection has been found to be predictive of acute EVD infection [11,12]. Other acute manifestations include subconjunctival hemorrhages and vision loss of unclear origin, which has been reported within an Ebola Treatment Unit (ETU) setting [11,12].

The first report of uveitis during disease convalescence arose from the 1995 Kikwit epidemic in the DRC. Twenty-one survivors were followed longitudinally for long-term complications. Four EVD survivors developed a spectrum of uveitis (anterior to posterior), 47–72 days after acute EVD. Treatment was initiated with topical 1% atropine and corticosteroids and led to disease resolution [11]. Although the clinical course was not specifically detailed in these four survivors, several retrospective series from the most recent West African outbreak have provided more detailed characterization of the eye disease phenotypes identified during EVD convalescence.

Evidence from the recent West African Ebola virus disease outbreak

Uveitis has specifically been identified as the most common ophthalmic manifestation and is observed in 13–34% of EVD survivors [13[■],14,15[■],16]. Table 1 summarizes the recent retrospective and prospective series describing ophthalmic manifestations in EVD survivors. Within a cohort of EVD survivors with ocular complications, we observed a spectrum of uveitis. Posterior and panuveitis were most commonly observed, occurring in 57 and 29% of patients with anterior uveitis occurring in 14% of patients (Figs. 1 and 2). Unilateral presentations were observed more commonly than bilateral disease. Vision was worse than 20/400 in 39% of affected eyes in this series from Liberia, underscoring potential for blinding complications that require urgent attention by the medical community [13[■], 14,15[■],16,18,19].

In another large, retrospective cohort study from Sierra Leone, a spectrum of uveitis was observed with anterior, posterior, pan-uveitis and intermediate uveitis occurring in 46, 26, 25 and 3% of eyes, respectively [14]. A prospective study noted anterior, posterior and pan-uveitis in 48, 28 and 8.7% of Guinean EVD survivors, with disease onset either at ETU discharge or within the first 2 months in more than 75% of identified patients [15[■]].

So far, in these uncontrolled cohorts, risk factors associated with the development of uveitis have included conjunctival injection and lower cycling threshold as determined by RT-PCR analysis during acute EVD [14,16]. Other EVD-associated ocular complications include neuro-ophthalmic disease including optic neuropathy and ocular motility disorders [13[■]].

The PREVAIL III study in Liberia is a National Institutes of Health sponsored, prospective cohort study that is longitudinally following ocular disease in EVD survivors and first-

degree close contacts of EVD survivors. Preliminary results show that 24% of survivors have signs of uveitis including posterior synechiae, anterior chamber cell, vitreous opacities, macular edema, retinal lesions, tractional retinal detachments and phthisis bulbi. Interestingly, their cohort had optic nerve swelling in 10% of EVD survivors and 5% of controls ($P=0.03$) with color vision deficits noted in 39% of survivors and 13% of controls ($P<0.001$) [17]. In this same study, younger age and increased time spent in an ETU conferred a greater risk of uveitis development with increased antibody response and viral persistence in testes conferring no increased risk [20].

Evidence from repatriated healthcare workers

Detailed case reports of uveitis during EVD convalescence in healthcare workers repatriated to the United States have also been described in the literature and have informed us about the pathogenesis of eye disease, including the role of viral persistence and systemic inflammation.

In one physician, unilateral anterior uveitis developed 40 days after his initial EVD illness and progressed to an anterior and intermediate uveitis. His vision declined to 20/200 and he was subsequently treated with topical and oral corticosteroids, as well as topical homatropine. The patient's visual acuity improved to 20/20 at final follow-up. Multiple laboratory abnormalities included HLA-B27 positivity and elevated ESR. Notably, IgM and IgG serologic positivity to cytomegalovirus, Epstein-Barr virus and varicella zoster virus, and detectable perinuclear antineutrophil cytoplasmic antibodies all resolved after corticosteroid treatment, suggesting broad but transient systemic immune activation [18].

We previously reported the development of unilateral, hypertensive anterior uveitis that progressed to a sight-threatening panuveitis in a repatriated physician, 10 weeks after he had recovered from acute EVD. The disease course was punctuated by severe eye pain, structural changes and sight-threatening sequelae including the rapid development of hypotony, iris heterochromia, retinal edema, optic neuropathy and a ciliary body/choroidal effusion. Prior to the development of acute uveitis, he was noted to have a bilateral posterior uveitis characterized by inactive-appearing chorioretinal scars [21].

During the acute episode of uveitis, an anterior chamber paracentesis was performed and tested positive for EBOV by RT-PCR (cycling threshold 18.7) and EVOB culture. The low cycling threshold suggested high levels of replicating virus and marked the first time that live EBOV virus had been isolated from the eye, implicating its pathogenesis in EVD-associated uveitis in this case. A conjunctival swab after the anterior chamber paracentesis tested negative for EBOV by RT-PCR reinforcing the important concept that there remained no known risk of transmission via casual contact (i.e. ophthalmic examination).

Therapies administered to this patient included topical corticosteroids, oral prednisone, oral favipiravir and a retroseptal triamcinolone acetate injection (40 mg/ 1 ml, Kenalog). The local corticosteroid injection was administered after 48 h of antiviral therapy, but the precise contribution of these therapies to the patient's recovery remains unknown. Ocular hypotensives were also administered during the hypertensive phase of the acute eye disease, but eventually were discontinued.

During an approximately 2-week period, the visual acuity nadir was hand motions and severe hypotony developed. After the above-mentioned treatments at critical time points throughout his disease course, vision eventually returned to 20/15 at 3 months follow-up [21].

Role of antiviral and anti-inflammatory therapies for Ebola virus disease-associated uveitis

Although there are no prospective studies assessing the efficacy of the treatment of EVD-associated uveitis, recent case reports and retrospective reviews suggest that treatment with topical and oral corticosteroids may be used in EVD survivors with a favorable response. Although one patient received the antiviral favipiravir during the development of acute uveitis [21], it is unknown whether its use expedited disease resolution or how generalizable its use would be to other EVD survivors with uveitis in West Africa and internationally.

One striking difference emphasizing the importance of timely diagnosis and treatment is related to the degree of vision impairment and blindness following severe disease observed in the two case reports of US physicians and the Liberian cohort of EVD survivors. Specifically, while both of the United States health care workers recovered vision following therapy [17[■],21], nearly 40% of eyes in the Liberian cohort had vision worse than 20/400 had their initial presentation, sometimes because of structural complications including cataract and dense vitreous opacity [13[■]].

This high level of severe vision impairment and blindness in West Africa EVD survivors is likely related to resource-limited delays in access to appropriate care, ultimately leading to a delay in uveitis diagnosis and effective treatment. If capacity were built for timely ophthalmic interventions in areas at-risk for EVD, this would likely reduce the risk of vision-related morbidity in future outbreaks.

VIRAL PERSISTENCE IN THE EYE AND IMMUNE-PRIVILEGED ORGANS

An emerging theme of this outbreak is the increased recognition and understanding of the potential for long-term EBOV persistence in immune privilege sites/organs. This has individual patient implications related to inflammatory syndromes (e.g. meningoencephalitis and uveitis) causing clinical disease in immune-privileged sites, public health ramifications related to transmission risk surrounding exposure to body fluids via sexual contact or invasive procedures and global health implications of the potential for EBOV persistence in immune-privileged sites in survivors and animal reservoirs. Underlying each of these are new scientific questions of the host–pathogen interaction that determines as EBOV persistence in immune-privileged sites.

EBOV was cultured from the aqueous humor of a patient during an episode of acute, unilateral hypertensive anterior uveitis, implicating direct lytic viral infection in disease pathogenesis [21].

The Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) study is currently underway in Sierra Leone and is evaluating the prevalence of persistent EBOV in the ocular fluids of survivors anticipating eye surgery. Preliminary results have demonstrated that

survivors who test negative for EBOV RT-PCR may undergo manual small incision cataract surgery with significant improvements in visual acuity [19,22]. The EVICT study will provide evidence that can guide the ophthalmic community related to invasive eye procedures in EVD survivors.

Besides the identification of EBOV RNA in the aqueous humor, recent descriptions of EBOV persistence in the central nervous system [23], placenta [24] and in semen up to 565 days postacute EVD [25] highlight the need to investigate the parameters of EBOV clearance from immune-privileged organs. There are documented or strongly suspected cases of EBOV transmission from sexual contact and breast feeding [26,27], which indicate new transmission chains. Understanding the mechanisms in which EBOV continues to persist in these sites will be important for targeted medical countermeasures and prevention of future outbreaks.

INSIGHTS INTO PATHOGENESIS FROM THE LABORATORY

Recent investigations in animal models and cell culture lines have provided novel insight into potential mechanisms of EBOV viral persistence and reactivation. Zeng *et al.* [28] recently described the detection of persistent EBOV infection in immune-privileged organs of rhesus monkeys that had received medical countermeasures or were rare natural survivors of high-dose EBOV infectious challenges. Specifically, EBOV was identified in the eye, brain and testes in monkeys that survived EBOV infection. CD68⁺ macrophages within the vitreous humor provided an EBOV reservoir within the eye, and ocular findings included uveitis, retinitis and gliosis.

Smith *et al.* [29] reported their finding that EBOV was capable of infecting human retinal pigment epithelial cells, which could subsequently support viral replication and release of virus in high titer. Although EBOV is known to shut down the type I interferon response as a mechanism of survival, human RPE cells infected with EBOV generated a robust type I interferon antiviral response. In addition, human RPE cells infected with EBOV simultaneously express immunomodulatory molecules. Thus, the interaction of EBOV and infected RPE cells may limit viral infection of neighboring cells, while allowing providing a protective environment for EBOV-infected RPE cells to evade immunologic detection.

The mechanisms by which EBOV production may be stimulated from low-level persistent EBOV infection and lead to clinical disease such as uveitis warrant investigation; however, studies in mouse and bat cell lines suggest that activation of stress-related pathways (i.e. Ras/MapK) may lead to EBOV reactivation from animal reservoirs following the establishment of viral persistence [30].

EBOLA THERAPIES, VACCINE AND FUTURE DIRECTIONS FOR EYE CARE

A number of medical countermeasures have been evaluated during this most recent outbreak through prospective clinical trials, as well as case series and case reports. Apart from the paramount importance of supportive care, medical countermeasures administered for acute EVD have included brincidofovir, convalescent plasma, ZMapp, small-interfering RNA and favipiravir [31].

Vaccination strategies have also been evaluated during this EVD outbreak including an open-label, cluster-randomized ring vaccination trial (Ebola ca Suffit!) in Guinea and Sierra Leone. This vaccine strategy utilized a recombinant vesicular stomatitis virus vaccine vector expressing a surface glycoprotein of Zaire EBOV (rVSV-ZEBOV) and showed that rVSV-ZEBOV offered substantial protection against EVD. Specifically, no cases of EVD were observed after 10 days of vaccination clusters of individuals (i.e. contacts of EVD patients and contacts of contacts) who received the vaccine [32■■■].

Whether these treatment strategies are relevant for eye disease in EVD survivors is unknown. Anti-inflammatory therapy with topical and systemic corticosteroids has been associated with disease resolution and vision recovery; however, whether a combination of antiviral and anti-inflammatory strategies may be important for survivors with viral persistence remains unknown

CONCLUSION

Our increasing recognition of the range of ophthalmic findings, experience with anti-inflammatory therapy to avert permanent ocular morbidity and increased understanding of EBOV persistence in the immune-privileged eye raise further questions about mechanisms of disease and highlight the importance of antiviral therapies for both acute disease and EBOV persistence.

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KEY POINTS

- Ophthalmic disease, specifically uveitis, is observed in an estimated 13–34% of EVD survivors.
- Eye disease occurs in the context of other systemic post EVD sequelae including arthritis, fatigue, abdominal pain and potential for viral persistence in immune-privileged sites.
- A spectrum of eye disease may be observed in EVD survivors ranging from anterior uveitis to sight-threatening panuveitis.
- Clinical and laboratory evidence suggests that pathogenesis of eye disease involves blood–ocular barrier breakdown and the potential for EBOV to persist in monocytes, macrophages and retinal pigment epithelium.

FIGURE 1. Slit lamp photograph shows the evidence of chronic, active anterior uveitis in an Ebola survivor. There are pigment deposits on a pupillary membrane at the inferior edge of the pupil and posterior synechiae.

FIGURE 2.

Slit lamp photograph shows a uveitic white cataract in an Ebola virus disease survivor with a history of panuveitis. There are posterior synechiae located superiorly.

Table 1

Case series reporting eye disease in West African Ebola virus disease survivors

References	No. of cases of uveitis/ total number of survivors (%)	Anatomic distribution of findings (%)	Visual acuity (VA) impairment	Notable findings
Shantha <i>et al.</i> [13 [■]]	21/96 (22%)	Anterior (10) Posterior (62) Panuveitis (29)	VA < 20/400 in 38.5%	Keratic precipitates, vitritis and chorioretinal scars associated with moderate vision impairment; optic neuropathy in three patients
Mattia <i>et al.</i> [14]	50/277 (18%)	Anterior (46) Intermediate (3) Posterior (26) Panuveitis (25)	–	Low cycling threshold during acute EVD associated with uveitis development; 10% with early cataract
Hereth <i>et al.</i> [15 [■]]	46/341 (14%)	Anterior (48) Posterior (28) Panuveitis (9)	15 (4.4%) with VA 6/12 (Snellen 20/40)	Most cases occurred within 2 months after discharge with relapses up to 13 months; 15% with complete cataract
Tiffany <i>et al.</i> [16]	57/166 (34%)	–	–	Conjunctival injection during acute EVD associated with uveitis development
Bishop <i>et al.</i> [17 [■]] (PREVAIL)	390 survivors and 174 controls evaluated; 24% of survivors with signs of uveitis	–	–	Optic nerve changes and color vision deficits greater in EVD survivors

EVD, Ebola virus disease.