Reflections on the Ebola Public Health Emergency of International Concern, Part 1: Post-Ebola Syndrome: The Silent Outbreak

Following the most recent outbreak of Ebola virus disease (EVD), the organized global effort brought new capabilities to postoutbreak clinical monitoring and surveillance. This, in turn, permitted a more robust analysis of post-EVD sequelae, resulting in better understanding of the so-called post-EVD syndrome (PEVDS).[1] Although it was previously established that PEVDS exists, factors affecting its duration and severity were not well known.[2] The pathogenesis of PEVDS was, and continues to be, poorly understood.[2] This knowledge gap is being addressed through a joint Liberia-US *Partnership for Research on Ebola Virus in Liberia* (PREVAIL) that was established in 2014.[3] PREVAIL will track 1500 survivors for up to 5 years to catalog long-term problems and try to better elucidate why individuals previously infected remain capable of transmitting the disease. It is now known at that approximately two-thirds of EVD survivors develop neurological complications and more than half experience ocular and musculoskeletal problems.[4] Similar investigations are being conducted in Sierra Leone[5,6] and in Guinea (funded by the French Ebola Task Force and the Institut de Recherche pour le Developpement).[7] With new discoveries, it its becoming increasingly evident that additional clinical, basic science, and epidemiological work will be required to ensure an in-depth understanding of EVD's pathophysiological sequelae.

Scientific Rationale for Post-ebola Virus Disease Syndrome

The rationale behind PEVDS is based on evidence that Ebola RNA persists in selected tissues during the convalescent phase.[8] The Ebola virus (EBOV) is present in saliva, tears, sweat, urine, semen, and cervical secretions.[9] Depending on the stage of the infection, the respective body fluids will also have varying levels of infectivity. The virus can also remain viable for extended periods (weeks) on various exposed surfaces and in deposits of dried biological materials.[10] In addition to direct evidence of persistent viral presence, it is highly likely that post-EVD state may result in immune-mediated sequelae similar to other viral ailments.[1] Manifestations of PEVDS include abdominal pain, alopecia, anorexia, fatigue, fever, arthralgias, cardiac manifestations, cough/dyspnea, cutaneous/rash, myalgias, hearing loss, blurred vision, headaches, sleep disturbances, uveitis, peripheral dysesthesias or paresthesias, short-term memory problems, erectile dysfunction, lethargy, and mood disorders (depression/anxiety).[1,2,6,7,11] In a recent large cohort study in Guinea, the most frequent symptoms were musculoskeletal pain (38%), headache (35%), abdominal pain (22%), ocular disorders (18%), and depression (17%).[7] A small proportion of patients reported various other neurological complaints, including "tremors," hemiparesis, and focal (e.g., facial) nerve palsies.[6] A recent report also suggests that late-onset encephalitis and polyarthritis can be seen among EVD survivors.[12]

Neurologic Manifestations

A broad range of neurologic conditions has been reported in association with PEVDS.[13] The exact relationship remains poorly understood, with some investigators suggesting that central nervous system (CNS) manifestations may be associated with factors such as cerebral hypoperfusion due to shock, viral encephalitis, or post-EVD encephalomyelitis.[13] It is likely that more than one factor is involved. Clinically, symptoms tend to be nonspecific (e.g., fevers, seizures).[13] Cerebrovascular accidents and encephalopathy have been described.[12,14] The more localized deficits noted among survivors include homonymous hemianopia which may be a result of stroke. Parkinsonian-like features with tremor, retropulsion, and changes in gait and muscle tone have been observed as well.[10] According to Bowen *et al*., difficulty with smooth pursuit movements, saccades, tremor, abnormal reflexes, abnormal sensory findings, and frontal release signs were the most common neurological findings in the 82 survivors examined.[15] Also noted were more severe neurological manifestations (e.g., hallucinations, meningitis, and coma).[15] Limited experiences with lumbar punctures suggest that EBOV-associated CNS findings may include both virus-negative and virus-positive (by reverse transcription polymerase chain reaction) cerebrospinal fluid (CSF) studies with elevated opening pressures.[13] Cerebral atrophy, ventriculomegaly, and evidence of hemorrhagic encephalitis may be seen on advanced imaging.[13] Delayed-onset meningitis and seizures have been reported, in some cases nearly 1 year after the initial infection.[13] Even more interesting, cross-correlative testing of blood and CSF demonstrated >99% homogeneity, strongly supporting the hypothesis of viral persistence.[13] It has also been postulated that the postviral syndrome may be related to increases in proinflammatory cytokines and an altered immune response creating a spiraling "cytokine storm."[10,16]

Immunologically privileged status of the CNS, because of the blood–brain barrier, may explain these persistent findings.[17] The heterogeneity of symptoms and their severity from the mild (headaches) to severe (encephalitis/meningitis) and the presence of both PCR virus-negative and virus-positive

results suggests a broader, more inclusive explanation. It is possible that there is a spectrum of disease that spans from the lower acuity "virus-free individual" who has a persistent autoimmune/inflammatory state,[18,19] to someone who harbors retained RNA as a continuous source of antigenic material causing a more intense level of symptoms, and finally the patient with the viral pathogen sheltered in the eyes and CNS, with active concern for disease recurrence.[20-24]

Other neurologic complaints associated with PEVDS include tinnitus and subjective hearing loss, affecting approximately 1 in 4 survivors.[12,24,25] However, further investigation has put these findings into question.[25] In addition, a small proportion of patients with PEVDS have reported altered sense of taste and smell, again without robust scientific validation.[26] Finally, some authors have speculated that children who recovered from acute EVD infection may be prone to subtle developmental delays.[13] The latter contention remains largely unproven and the key reason for any potential cognitive deficits in both children and adults may be the presence of hemodynamic collapse and cerebral hypoperfusion during the acute clinical phase of Ebola infection.

Nonneurologic Manifestations

In one study examining nonneurologic complaints, 11% of patients experienced cough; 9% reported chest pain, abdominal pain, or itching; and 7% reported fever, lack of appetite, or sleep-related difficulties.[6] Among gastrointestinal complaints, patients reported weight loss, poor appetite, diarrhea, vomiting, and epigastric pain.[6] A broad range of upper and lower respiratory complaints was reported as well, including nasal congestion, sneezing, shortness of breath, and chest pain.[6] Finally, nonspecific cutaneous complaints included rash, dry/flaky skin, "fever blisters" or "cold sores," ear pain, hiccups, and scrotal swelling.[6]

Day by day, researchers are learning more about PEVDS. An outstanding example in this area is the PREVAIL study in Liberia, which will track some 1500 survivors for up to 5 years, in an effort to categorize the long-term consequences of Ebola and assess the extent to which previously infected individuals remain contagious. Preliminary findings indicate that 68% of survivors suffer from neurological complications, 60% experience ocular problems, and 53% report musculoskeletal complaints.[4] Another recently published multidisciplinary observational cohort study was conducted across four sites in Guinea.[7] Most common symptoms reported by study participants included generalized complaints (40% of patients), musculoskeletal pain (38%), headaches (35%), depression (17%), abdominal pain (22%), and ocular disorders (18%). Furthermore, adult patients were more likely to suffer from multiple symptoms, ocular complications, and musculoskeletal symptoms.[7]

When compared to the current knowledge of the organic post-EVD complications, the understanding of various psychological sequelae among survivors represents an even greater challenge. While problems such as social stigmata, fear of illness reactivation, sleep disturbances, and other mental health issues are not uncommon after critical illnesses associated with prolonged ICU stays,[27] it remains to be determined whether these complaints are a consequence of significant neurological or physiologic injury, or a function of posttraumatic stress disorder. It is likely that clinical manifestations observed by researchers are due to a combination of both physical and psychological factors.

Ophthalmologic Manifestations

In addition to concerns about PEVDS manifestations discussed above, up to and including EVD recurrence, another important consideration is the presence of ophthalmologic manifestations among EVD survivors. Ocular symptoms were noted in approximately 60% of patients in a study from Sierra Leone, examining 277 survivors seen at a mean interval of 121 days following discharge from post-Ebola treatment unit(s). About 18% of these patients experienced uveitis as well.[10,28] Of note, latent EBOV infection has been described in ocular fluid of an EVD survivor. The latter occurrence was noted in the aqueous humor of the eye in a case of "sight threatening" panuveitis.[23] One pathological study evaluated swelling of the left upper eyelid and conjunctiva in a nonhuman primate following EBOV intramuscular challenge. Here, histological lesions with strong EBOV antigen staining were observed in the eye (scleritis, conjunctivitis, and perioptic neuritis), brain (choriomeningoencephalitis), stomach, proximal duodenum, as well as in the pancreas.[29] Cumulatively, many EVD survivors experienced both subjective and objective ophthalmologic symptoms, including conjunctivitis, conjunctival hemorrhages, uveitis, excessive lacrimation, and varying degrees of visual loss.[29-31] In this context, appropriate screening and surveillance programs should be instituted for survivors, including multidisciplinary evaluations consisting of musculoskeletal, neurologic, psychological, and rheumatologic assessments.[2] In terms of the need for post-EVD follow-up, it is important to note that during the outbreak in Uganda, approximately 25% of patients continued to report to clinic as long as 1 year following the infection.[6]

Research and Therapeutics

Treatment for the PEVDS is currently supportive and there is no definitive cure. Beyond recognizing the clinical features that are manifested as part of PEVDS, efforts must shift toward therapeutic measures that might be initiated during acute infection to minimize the incidence and severity symptoms among survivors. In addition, the scientific community must focus on effective therapeutic measures that may be useful in managing symptoms of PEVDS. Since the pathogenesis of the PEVDS is thought to be related to systemic injury resulting from the original infection, a sustained immune response, autoimmune-like inflammatory state, and viral persistence in specific anatomical locations (i.e., eye, brain, testes), treatment strategies directed at the inflammatory cascade and the immune

system may represent a good starting point in the quest for new therapies.[32] Toward this end, the National Institute of Allergy and Infectious Diseases initiated the PREVAIL III trial[33] in 2015 to facilitate long-term follow-up of survivors and household contacts in Liberia. From this group, they are recruiting subjects for the PREVAIL IV trial, which will examine the ability of an experimental compound, GS-5734, to clear persistent EBOV RNA from the semen in male survivors.[34] In addition to these efforts, a call has been made proposing therapeutic trials of cannabidiol, which has been hypothesized to improve inflammatory-mediated symptoms in a number of chronic medical conditions.[32,35] In this context, a group of researchers have suggested that Cannabidiol, a phytocannabinoid compound derived from *Cannabis sativa*,[32] may offer multiple beneficial properties in humans including anti-inflammatory, anti-anxiety, antinociceptive, and anticonvulsant actions in addition to treating insomnia.[35] However, it has been emphasized that a properly designed and conducted clinical trial must be performed first to determine the efficacy and safety of the proposed cannabidiol treatment.[32] Finally, the development of a highly effective vaccine against EBOV brings the hope of long-term sustainable containment of this deadly virus.[36,37]

Concluding Remarks

PEVDS in survivors of an Ebola outbreak poses a significant threat to the general health and quality of life in a population that has already suffered greatly. Care for this group of patients should be multidisciplinary, focused on long-term health maintenance, and quality of life optimization. The PEVDS continues to be poorly understood and deserves further research. Despite clinical improvement in most cases, there is mounting evidence to support persistent viral presence for extended periods of time.[2,6] In a large cohort, approximately 1 in 20 male survivors were found to have virus in their semen, with 1 patient still testing positively nearly 550 days after disease onset.[7] Since symptoms of PEVDS can persist for years, it has been suggested that survivors should be closely monitored for up to 18 months after clinical recovery from the acute infection.[7,38] Given the wide variety of symptoms, multidisciplinary assessment of these survivors is essential.[7,38] This will be particularly challenging as the health care systems in Guinea, Liberia, and Sierra Leone recover from the EBOV outbreak.[39] We expect to gain more insight into the clinical course of PEVDS from the PREVAIL study which is expected to follow 1500 Liberian EVD survivors and 6000 of their close contacts for up to 5 years.[40]

While our understanding of PEVDS pathogenesis must improve, medical advancements that make the recovery process easier for survivors are also urgently needed. The appearance of late-onset neurologic and rheumatologic manifestations highlights the need for better understanding of key virologic and inflammatory aspects of PEVDS.[12] The syndrome has been associated with worse functional outcomes and was noted to cause delays in return to work.[1] Consequently, calls have been made for neurocognitive impairment screening and allocation of appropriate resources for high fidelity neuroimaging for affected survivors.[12] Ongoing neurological, rheumatological, and ophthalmological follow-up is strongly advised based on growing evidence of viral persistence and various associated long-term sequelae. As such, PEVDS has the potential to be a "silent" source of disability among those who were fortunate enough to survive the primary, acute episode of infection.

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