**Post Ebola Syndrome: it’s not going away.**

**Janet T. Scott and Malcolm G. Semple**

The Ebola Virus Disease (EVD) Epidemic, 2013-2016 resulted in ~28 616 cases and left ~17 000 survivors [1]. Researchers, pulled globally from other projects, functioned on an emergency footing in the midst of the humanitarian disaster. We benefited hugely from previous research in this field, albeit carried out by teams working in difficult funding environments. However the sheer numbers of patients, meant that much of what we encountered about Ebola was new: the extent, longevity and complexity of post-Ebola syndrome (PES) [2, 3], mild or asymptomatic disease[4], persistent viraemia [5], sexual transmission[6], and recrudescence[7]. This outbreak taught us that research can and must be integrated into the harshest of circumstances in order to benefit patients in real-time. Fully exploiting the information gained, now the immediate emergency is past, is necessary to fully delineate and act on the ‘lessons learnt‘ [8].

The PostEboGui study, reported in this edition, is a good example[3]. It is a comprehensive multi-disciplinary longitudinal study of 804 EVD survivors in Guinea over a 27 month period post discharge. This cohort included 158 children aged from 1 to 18, (median 11yrs old). 76% of patients presented with post-EVD symptoms, a median one-year after discharge. Most frequent symptoms were “General” (fatigue fever and anorexia) (40%), musculoskeletal pain (38%), headache (35%), depression (17%), abdominal pain (22%) and ocular disorders (18%). Positive Ebola RT-PCR was found in 5% of adult men at a maximum of 548 days after disease onset measured using both the standard RealStarFilovirus Screen RT-PCR kit 1·0 and an in-house technique targeting the viral nucleoprotein.

A picture is now emerging of post-Ebola Syndrome (PES). Pain appears to be a dominant symptom – musculoskeletal, abdominal, or headache, as are psychosocial issues and ocular problems. Pain is subjective, however our impression is that these problems are related to Ebola. As controlled studies emerge this issue is likely to further clarify. The PostEboGui cohort[3] and similar studies underline that for many PES patients, problems continue well after the acute illness. Might we learn from other conditions to improve current management strategies [9]?

Ebola is not unique in predicating post viral consequences. One notable example is Chikungunya [10]. 20% of Chikungunya patients are left with a post viral chronic inflammatory joint disease. Chronic synovitis from virus infected joints, or the virus acting as a pro-inflammatory stimulus have been postulated for post-Chikungunya rheumatic disease. Such patients have responded well to methotrexate or anti-TNF therapies [11]. These drugs may prove problematic in fledgling health care settings, however Sulphasalazine, which is an oral therapy which requires minimal monitoring, might be a potential choice for PES.

Some aspects of PES mimic those of Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME), a debilitating and complex disease characterised by prolonged and disabling fatigue. The range of CFS/ME symptoms include; headache, muscle/joint pain, and post-exertional malaise [12]. The aetiology and pathophysiology of CFS/ME is not yet determined. Current areas of investigation include infection and inflammation as well as altered immunity. Evidenced based treatment programs include graded exercise and cognative behaviour therapy. Symptomatic pain relief can include tricyclic antidepressants such as amitriptyline. Might inspiration be taken from this approach for PES?

The paediatric cohort in the PostEboGui study may provide insight into the development of PES. Although their CT values (a proxy measure for viral load) was similar on diagnosis of their acute illness compared to adults, they suffered less during the acute phase of their disease and subsequently reported fewer clinical events or specific PES symptoms. On the other hand general signs and psychological distress were more common in the paediatric cohort. This pattern was also seen when younger and older children were compared. Are those children who survived more resilient than adults? Or is it that children only survived if they had milder symptoms in the acute phase? Unfortunately, we can’t discriminate with this data.

After all that Ebola survivors have been through, the final insult appears to be that they may not, after all, be considered safe. Recrudescence can occur [7], and that although transmission events have been extremely rare, in a few adult men semen remains RT-PCR positive up eighteen months later. This implies that sexual transmission remains a risk. 40% of patients in the PostEboGui cohort reported ‘general symptoms’ including fever: is this concerning? Fever is a common symptom in West Africa with many causes including malaria. These fevers are often treated empirically. An agreed protocol for screening for potential recrudescence (which may be mild) would be prudent. We applaud efforts to instigate access for EVD survivors to quality health care, including adequate diagnostic tests. This is not only a humanitarian act, but is needed for public health surveillance.

The PostEboGui study covers a wide variety of disciplines from psychosocial assessment to virological analysis of body fluids. This reflects the wide range of challenges that remain in Ebola. The research effort is not over.

808 words

JTS MGS

1. *WHO Situation Report Ebola Virus Disease.* 2016.

2. Scott, J.T., et al., *Post-ebola syndrome, Sierra Leone.* Emerging Infectious Diseases, 2016. **22**(4): p. 641-646.

3. jean-françois etard, M.D., Ph.D; mamadou saliou sow, M.D; sandrine leroy, M.D; abdoulaye touré, PhD; bernard taverne, M.D; alpha kabinet keita, M.D.,Ph.D; philippe msellati, M.D.,Ph.D; N'Fally Magassouba, PhD; Sylvain Baize, PhD; Hervé Raoul, PhD; suzanne izard; cécé kpamou; laura march; ibrahima savane, M.D; moumié barry, M.D; Eric Delaporte, M.D.,Ph.D, *Multidisciplinary assessment of post-Ebola sequelae: an observational cohort study in Guinea (PostEboGui).* Lancet Infectious Disease, 2016.

4. Glynn JR\*, B.H., Johnson S, Houlihan C, Montesano C, Scott JT, Semple MG, Bangura MS, Kamara AJ, Kamara O, Mansaray SH, Sesay D, Turay C, Dicks S, Guetiya Wadoum RE, Colizzi V, Checchi F, Samuel D¶, Tedder RS *Asymptomatic infection and unrecognised Ebola Virus Disease: prevalence of Ebola virus sero-positivity in a large survey in Ebola-affected households, Sierra Leone, using a new non-invasive assay*

*.* submitted Lancet Infectious Disease.

5. Brainard, J., et al., *Presence and Persistence of Ebola or Marburg Virus in Patients and Survivors: A Rapid Systematic Review.* PLoS Neglected Tropical Diseases, 2016. **10**(2).

6. Diallo, B., et al., *Resurgence of Ebola Virus Disease in Guinea Linked to a Survivor with Virus Persistence in Seminal Fluid for More Than 500 Days.* Clinical Infectious Diseases, 2016. **63**(10): p. 1353-1356.

7. Jacobs, M., et al., *Late Ebola virus relapse causing meningoencephalitis: A case report.* The Lancet, 2016.

8. Gates, B., *The Next Epidemic — Lessons from Ebola.* New England Journal of Medicine, 2015. **372**(15): p. 1381-1384.

9. WHO, *Clinical care for survivors of Ebola virus disease.* 2016.

10. Win, M.K., et al., *Chikungunya fever in Singapore: Acute clinical and laboratory features, and factors associated with persistent arthralgia.* Journal of Clinical Virology, 2010. **49**(2): p. 111-114.

11. Blettery, M., et al., *Brief Report: Management of Chronic Post-Chikungunya Rheumatic Disease: The Martinican Experience.* Arthritis & Rheumatology, 2016. **68**(11): p. 2817-2824.

12. Baker, R., E.J. Shaw, and G. Guideline Dev, *Guidelines - Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephabpathy): summary of NICE guidance.* British Medical Journal, 2007. **335**(7617): p. 446-448.