Disability among Ebola survivors and their close contacts in Sierra Leone: a retrospective case-controlled cohort study.

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**Abstract**

Ebola survivors [21/27 (77.8%)] suffer more disability than their close contacts [6/54 (11.1%), (aOR 23.52; 95%CI 6.46-85.67; p<0.001)] when measured by Washington Group-Disability Extended Questionnaire. Major limitations in vision, mobility, cognition, and affect were observed in survivors one year following the 2014-6 Ebola outbreak, highlighting the need for long-term rehabilitation.

**Background**

The scale of the 2014-6 West African Ebola outbreak has resulted in an unprecedented number of survivors and the opportunity to vastly improve the understanding of the health challenges they face (1). In early convalescence from Ebola Virus Disease (EVD), ocular, musculoskeletal and neuropsychiatric sequelae are common (2-5). Reports from the Bundibuygo and Kikwit outbreaks suggest there are also long-term complications (6, 7). Difficulties of survivors in resuming work after EVD were reported following the Gulu outbreak in Uganda (8).

We assessed disability amongst a cohort of EVD survivors 12 months following their discharge and compared with their close contacts in Freetown, Sierra Leone.

**Methods**

We recruited study participants in June 2016 by systematic sampling from a list of attendees at the Ebola Survivors Clinic, 34 Military Hospital (MH34) in Freetown, Sierra Leone. Based on background disability surveys from Sierra Leone (9) and data from EVD cross-sectional studies, 50% of survivors were estimated to have one or more form of disability compared with 17% in the general population. A total sample size of 81 (27 EVD survivors and 54 contacts) was estimated as being required to detect a difference of this magnitude or greater with 80% power using a conventional two-sided significance level of 5% (GPower 3.1, formula based on Fisher exact test). Inclusion criteria for EVD survivors were: confirmed EVD by PCR testing, age over 19 years, completion of 12 or more months of convalescence at the time of recruitment, and verification of an EVD discharge certificate. Each EVD survivor recruited was requested to bring two close-contacts (1:2) from during the time of disease, preferably members of their family, who had never been admitted to an Ebola treatment unit, and were not enrolled in an EVD vaccine trial. All close-contacts recruited as controls were from the same community as cases at time of disease, same language group, and similar socio-economic status as the cases.

Disability was measured using the Washington Group-Disability Extended Questionnaire (WG ES-F) for both the EVD survivors and their non-affected contacts. The questionnaire measured self-reported physical and mental impairments present at the time of the interview (See Supplementary Material). The questionnaire assesses six domains: vision, hearing, mobility, self-care, communication and cognition. Functionality scores were calculated from the severity and frequency of anxiety, depression, pain and fatigability. We conducted face-to-face interviews in Krio and English and recorded the responses in an electronic format of the questionnaire.

Categorical disability measures were summarised using frequency counts and percentages; differences between the exposed (survivor) and unaffected contacts (control) subjects were summarised as odds ratios with their exact (binomial) 95% confidence intervals, after adjustment for age and sex using logistic regression (aOR). Continuous disability measures were summarised using means and standard deviations; differences between the exposed and unexposed subjects were summarised as mean differences with their 95% confidence intervals, after adjustment for age, sex, and occupation using linear regression. The other demographic factors (including place of residence) did not contribute as confounding factors during statistical modeling. All statistical tests were two tailed, with significance set at the conventional 5% level. All analyses were done using Stata™ 14.

All participants provided written informed consent. The protocol was approved by the institutional ethics review board of The Liverpool School of Tropical Medicine, UK (10th May, 2016), and the Sierra Leone Ethics and Scientific Review committee (31st May, 2016).

**Results**

Twenty-seven EVD survivors (cases) and 54 unaffected contacts (controls) were recruited. The EVD survivors were more likely to be over 25 years of age (n=21; 77.8%) than the controls (29; 53.7%) and to be female (n=21; 77.8% vs. 29; 53.7%) (Fisher exact test p=0.05 for both). At the time of the study EVD survivors were less likely to live in the Western Urban area, outside Freetown (n=11; 40.7% vs. 36; 66.7%: Fisher exact test p=0.03) and more likely to be unemployed due to health reasons (n=4; 14.8% vs 0: Fisher exact test p=0.01). There was no significant difference in pre-existing co-morbidities between the two groups at a median time of 18 months post-discharge.

Disability in at least one of the six functional domains was reported by significantly more EVD survivors than controls (aOR 23.5; 95%CI 6.5-85.7) (Table 1). EVD survivors had higher odds of blurred vision (aOR=7.6; 2.0-27.9). Subjective hearing loss was observed (OR=12.05; 1.31-110.6, p=0.03) but this was not statistically significant when adjusted for age (aOR=11.5; 0.6 – 214, p=0.1). Differences in physical disability were most marked with the survivors cohort being more likely to experience difficulty in walking 100m, 500m, climbing 12 stairs and “moderate disability in mobility” than controls (aOR for each ranging 64 to 206, all p<0.001).

Self-rated levels of pain, fatigue, anxiety and depression influenced disability in mobility. Relative to controls the EVD survivors had a very significantly increased mean pain scores (adjusted mean difference 2.51; 95% CI 1.33 - 3.69), fatigue scores (2.23; 1.36 - 3.09), anxiety scores (1.89; 0.52 - 3.27) and depression scores (3.32; 1.95 - 2.59). Mean fatigue scores were significantly higher for female than for male EVD survivors (3.12; 0.88 - 5.36; p=0.008) but were similar for the two sexes among the controls (0.05; -0.37 - 0.48; p=0.799). No EVD survivors or contacts reported disturbances in self-care and communication.

When compared to their controls, EVD survivors had significantly higher subjective difficulties remembering or concentrating (9/27, 33.3% vs 0; p<0.001).

**Discussion**

This study provides case-controlled data on disability in EVD survivors, showing that they have higher odds of developing disability in vision, mobility and cognition one year after recovery from acute disease in comparison to their contacts.

We observed that mobility limitation was the most common post-Ebola disability in EVD. The survivors reported significantly higher odds of limitations in walking 500m and climbing stairs. Musculoskeletal pain was the major contributor to mobility limitations. Our findings reporting long-term musculoskeletal pain concur with the studies from Kikwit and Bundibuygo (6, 7).

We also observed that survivors of EVD are more likely to have blurred vision than their contacts. Ocular sequelae have been demonstrated in survivors from West Africa (4, 10) and require specialist assessment and in the long-term cataract replacement is frequently indicated. We did not observe a statistically significant difference in self-reported hearing loss between the two groups. The evidence from the 1995 EBOV outbreak shows that the post-EVD complaint of hearing loss was not significant by audiometry, 21 months following the outbreak (7). Subjective hearing loss described in studies (2, 4) during early convalescence may recover within months as it can with Lassa fever (11).

The psychological effects of EVD are often neglected in the acute setting, but would be expected to persist into convalescence and may compound physical disabilities. Our data showed that the adjusted odds ratios of depression and anxiety were significantly higher in EVD survivors, compared to controls and that a third of survivors also had significant difficulties with concentration. This subjective post-EVD cognitive impairment coincides with the short-term memory problems that have been reported in earlier studies (5, 12). This may be sequelae of critical illness or suggest direct viral neurological involvement.

The main limitation of the study is dependence on self-reporting of disabilities. We mitigated this by design using a validated questionnaire with objective measurements of disability and community controls. The selection of controls (contacts not affected by EVD) by the survivors may have introduced some bias, although 22% did have evidence of disability, consistent with previous population estimates (9). We were unable to screen serologically for asymptomatic EVD infection in the control group. However, asymptomatic EBOV infection has recently being shown to be uncommon in Western area, Sierra Leone even in close contacts (13). Although adequately powered, the study sample size was small, resulting in wide confidence intervals. This study only focused on the investigation of disability in adults, whereas paediatric survivors remain an important understudied and vulnerable group. Despite these limitations, the study provides statistically significant case-controlled evidence on post-Ebola disability in EVD survivors using a standardised disability questionnaire.

Further research in this cohort is required to understand the pathogenesis of sequelae and characterise disability further. It is clear that EVD survivors require an integrated package of care. Long-term treatment and rehabilitation strategies are challenging in the context of a constrained health system but require advocacy, investment, and a holistic approach. Specific interventions such as physiotherapy have been reported to be effective in post-Chikungunya disease (14), and might benefit EVD survivors. Task shifting of rehabilitation services to community-based rehabilitation programmes for identifying disability and accessing assistive devices may prove an effective strategy. Displacement of survivors from their communities following the outbreak remains a concern that needs to be explored.

This study has demonstrated that a year following acute disease, survivors of the recent EVD outbreak have higher odds of persisting disability in mobility, vision, and cognition. Mental health issues such as anxiety and depression persist in EVD survivors and must not be neglected. Further evaluation of the scale of disability in larger survivor cohorts is required, as is a new focus on sustainable long-term rehabilitation in EVD survivors.

Word count: 1500

Notes

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**Table I: Comparison of disability between the EVD survivors (cases) and unaffected contacts (controls).**

|  |  |  |  |
| --- | --- | --- | --- |
| **Comorbidities and limitations measured** | **Cases** | **Controls** | **Odds Ratio (95% CI) [p]** |
| **Unadjusted** | **Adjusted** |
| Sample size | 27 | 54 |  |  |
| Pre-existing comorbidities reported | 4 (14.8%) | 3 (5.6%) |  2.96 (0.61 - 14.43) [p=0.180] |  1.55 (0.33 - 7.19) [p=0.579] 1 |
| Some disability | 21 (77.8%) | 6 (11.1%) | 17.85 (8.02 - 97.74) [p<0.001] | 23.52 (6.46 - 85.67) [p<0.001] 1 |
| Disability with long-distance vision |  7 (25.9%) | 3 (5.6%) |  5.95 (1.39 - 25.54) [p=0.016] |  6.65 (1.53 - 28.88) [p=0.011] 1 |
| Disability with near-distance | 11 (40.7%) | 4 (7.4%) |  8.59 (2.38 - 31.01) [p=0.001] | 10.31 (2.75 – 38.58) [p=0.001] 1 |
| Blurred vision | 12 (44.4%) | 5 (9.3%) |  7.84 (2.36 - 26.04) [p=0.001] |  7.55 (2.04 – 27.93) [p=0.002] 1 |
| Subjective hearing disability |  5 (18.5%) | 1 (1.9%) | 12.05 (1.31 - 110.6) [p=0.028] | 11.47 (0.62 - 213.8) [p=0.102] 1 |
| Limitations in walking 500m | 20 (74.1%) | 2 (3.7%) | 74.29 (14.07 - 392.3) [p<0.001] | 94.30 (11.73 - 757.8) [p<0.001] 1 |
| Limitations in climbing 12 steps | 23 85.2%) | 4 (7.4%) | 71.87 (16.35 - 315.9) [p<0.001] | 64.76 (13.68 - 306.6) [p<0.001] 1 |
| Minimal disability in mobility | 23 (85.2%) | 4 (7.4%) | 71.87 (16.35 - 315.9) [p<0.001] | 64.76 (13.68 - 306.6) [p<0.001] 1 |
| Moderate disability in mobility | 18 (66.7%) | 1 (1.9%) | 106.0 (12.38 - 907.6) [p<0.001] | 205.6 (19.95 - 2119.) [p<0.001] 1 |
| Severe disability in mobility | 4 (14.8%) | 0 | [0.011]\* | ---\*\* |
| Difficulty in self-care | 0 | 0 | ---\*\* | ---\*\* |
| Difficulty in communication  | 0 | 0 | ---\*\* | ---\*\* |
| Difficulty remembering/concentrating | 9 (33.3%) | 0 | [<0.001]\* | ---\*\* |
| Pain score | Mean (SD) | 4.07 (2.69) | 0.89 (1.70) | 3.18† (2.21 - 4.16) [p<0.001] | 2.51† (1.33 - 3.69) [p<0.001] 2 |
| Fatigability score | Mean (SD) | 3.26 (2.65) | 0.39 (0.76) | 2.87† (2.10 - 3.64) [p<0.001] | 2.23† (1.36 - 3.09) [p<0.001] 2 |
| Anxiety | Mean (SD) | 3.37 (3.49) | 1.04 (1.60) | 2.33† (1.21 – 3.46) [p<0.001] | 1.89† (0.52 - 3.27) [p=0.008] 2 |
| Depression | Mean (SD) | 5.07 (4.19) | 0.96 (1.35) | 4.11† (2.87 – 5.35) [p<0.001] | 3.32† (1.95 - 2.59) [p<0.001] 2 |

***1: adjusted for age and sex 2: adjusted for age, sex and occupation †: mean difference in scores***

1. ***\* : odds ratios not calculable – Fisher exact test p-value \*\* : odds ratios not calculable***

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