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Review

Neuropsychological long-term sequelae of Ebola virus disease survivors – A systematic review

Felix Lötsch, Jenny Schnyder, Abraham Goorhuis, Martin P. Grobusch Prof *

Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, The Netherlands

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ABSTRACT

Background: The recent West African Ebola virus disease (EVD) outbreak had catastrophic impact on populations, health care systems and economies of the affected countries. Somatic symptoms have been reported to persist long beyond the acute infection. This review was conducted to provide an overview on neuro- and socio-psychological long-term sequelae of EVD survivors.

Methods: Utilizing Pubmed and PsycInfo databases, a systematic review prepared according to PRISMA guidelines. Only studies reporting quantitative data on neuropsychological sequelae three weeks or later after discharge from the Ebola-treating unit were included. Pooled proportions of common outcomes were calculated.

Results: In total, 224 papers were identified, of which 10 were included. Depression, insomnia, fatigue, anxiety and post-traumatic stress were common sequelae in EVD survivors. However, data from high-quality studies were scarce.

Conclusions: EVD survivors have been thought to commonly face neuropsychological long-term sequelae. Methodological drawbacks and heterogeneity of current studies limit conclusions of the impact and magnitude of such sequelae. We advocate the preparation of a prospective, controlled cohort study protocol in preparation for a future outbreak.

1. Introduction

The recent Ebola outbreak in West Africa, mainly affecting Guinea, Liberia and Sierra Leone, has had catastrophic impact on the affected patients, health care systems and countries, but has also led to the development of vaccines [1,2]; allowed the evaluation of interventions [3,4]; and provided new insights into Ebola virus disease (EVD) and its consequences [5]. Now, in the aftermath of the epidemic, there are over 10,000 survivors according to the WHO [6]. The long recovery period of EVD was already noted during the outbreak in Sudan in 1976 [7], and prolonged psychological problems were acknowledged after the Uganda outbreak in 2001 [8]. As recently reviewed by Vetter and colleagues, EVD survivors frequently struggle with long-term sequelae such as rheumatologic, ocular or neurological disorders [5]. However, patients do not only suffer from somatic complaints but also from neuropsychological sequelae and stigmatization after discharge from the Ebola treating unit (ETU). The aim of this review was to provide a concise overview of published data on neuro- and socio-psychological sequelae and to summarize the data on frequencies and proportions of such complications in Ebola survivors.

2. Methods

A systematic literature search in line with PRISMA guidelines was performed in PubMed and PsycINFO using “Ebola” AND (“sequelae” OR “convalescent” OR “survivors”) as search terms. Studies indexed up to January 30th, 2017 were included. No other restrictions on publication date or language were applied. After exclusion of double entries, two researchers (JS, FL) independently assessed all publications. Studies were included if neuro- and socio-psychological sequelae or stigmatization of survivors of a confirmed or probable Ebola virus disease were reported quantitatively 3 weeks (or more) after discharge. Reference lists of included studies were also reviewed for potentially relevant articles that were missed in the database search. Data was extracted by one author and double-checked by another in a self-designed data

* Corresponding author.
E-mail address: m.p.grobusch@amc.uva.nl (M.P. Grobusch).

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extraction form. Authors were contacted if important information was missing. Data was extracted for all neuro-psychological and psychosocial sequelae presented in the included studies Simple pooled analysis was performed for the outcomes 'depression', 'insomnia' and 'fatigue'. No other summary measure was used. Bias evaluation of individual studies was performed using the original Newcastle Ottawa scale for cohort studies and a modified version for cross-sectional studies (Supplementary Materials 1,2; Supplementary Tables 1–3). No bias evaluation was performed for case-series, short reports without a method section and qualitative studies reporting quantitative data only as secondary outcome. No bias evaluation was performed for bias across studies. The review protocol was registered with the University of Amsterdam.

3. Results

The search yielded 224 articles in total, of which 10 studies were included in this review. A flow chart depicting the study selection process is presented in Fig. 1. Eight studies stem from the recent outbreak in West Africa; one study from the 1995 outbreak in Kikwit, Democratic Republic of Congo, and one from the 2007 outbreak in Bundibugyo, Uganda. All studies were published in English.

Four studies providing information on the interval between discharge and assessment reported data on depression in EVD survivors [9–12]. The largest of these studies by Etard et al. used previously evaluated questionnaires and scales and found 124 out of 713 participants (17%) to suffer from symptoms that may be indicative for depression at study inclusion. The median delay between study inclusion and discharge from the Ebola-treating unit was 350 days (IQR 223–491). Follow-up in this prospective study is ongoing, and has not been published to date [9]. Only one study compared depression in Ebola survivors with a seronegative control group. The authors found a depressed mood in 12/49 (24%) survivors compared to 23/157 (15%) in the control group (RR 1.9; 95% CI 1.0–3.6; p = 0.058) 29 months after the outbreak. The authors also performed a sensitivity analysis including probable cases, whereupon the results achieved statistical significance. Data were collected retrospectively [13].

In a cross-sectional study by Qureshi et al., 34/104 (33%) patients described a difference in mood; in one patient (1.0%), self-perceived depression was documented [10]. The median time between discharge and assessment was 103.5 days (SD 47.9). In another cross-sectional study from Sierra Leone, Nanyonga et al. assessed long-term sequelae four months or later after resolution of the acute disease in a convenience sample of 81 survivors. Depression was recorded in 30/81 (37%) survivors. However, no details on the methods of data collection and tools used for assessment were provided in this report [11].

In a case series of American survivors, 'depression or anxiety' was reported in 4/8 (50%) of patients. Symptoms started 0–12 weeks after discharge and lasted 4 weeks. A semi-structured questionnaire by phone or face-to-face was used to evaluate patients [12]. A summary of frequency of depression across these four studies is presented in Fig. 2.

Mohammed et al. assessed psychological distress in Ebola survivors using the General Health Questionnaire. Four survivors were included and two (50%) reported that they had been feeling unhappy or depressed [14]. In a study with survivors from Sierra Leone, an attempt to assess long-term sequelae was made by reviewing medical charts. Mental health counselling and depression was recorded in 2 out of 115 survivors. However, the authors state that this was not recorded consistently in the medical charts and that the numbers probably underestimate problem [15].

Another common symptom was insomnia, which was reported in seven studies [10–16]. In a retrospective cohort study with survivors of the outbreak in Bundibugyo, Uganda, and a control group, symptoms were assessed using a standardized questionnaire; 28/49 (57%) individuals reported difficulties sleeping. Sleeping difficulties were significantly more frequent in survivors compared to the controls (RR 1.9, 95%CI 1.3–2.8; p < 0.001) 29 months after the outbreak [13]. In the recent outbreak, insomnia was recorded in 55/115 (48%) survivors in Sierra Leone at one point during the follow-up. The data were extracted retrospectively from medical charts and records [15]. In a similar study by Tiffany et al. based on routine data from a survivor clinic 20/104 (19%) of survivors presenting 30 days or later after discharge from the ETU to a survivor clinical reported insomnia [16].

Qureshi et al. reported insomnia in 13/104 (13%) and difficulty sleeping in 20/105 (19%) survivors in a cross sectional study using a self-designed questionnaire [10]. Nanyonga et al. found 34/81 (42%) survivors suffering from sleeplessness, although it is not described how the symptoms were assessed [11]. Out of the eight American survivors who were interviewed after convalescence, 4 (50%) reported insomnia. In one additional patient, it had already resolved at the time of assessment [12]. Furthermore, 3/4 (75%) survivors in Nigeria reportedly had lost much sleep over worry [14] (see Fig. 3).

In a prospective cohort study from Kikwit, Democratic Republic of the Congo, extreme fatigue was recorded 10 times in 123 contacts (8%) with 29 survivors throughout a 6-month follow-up

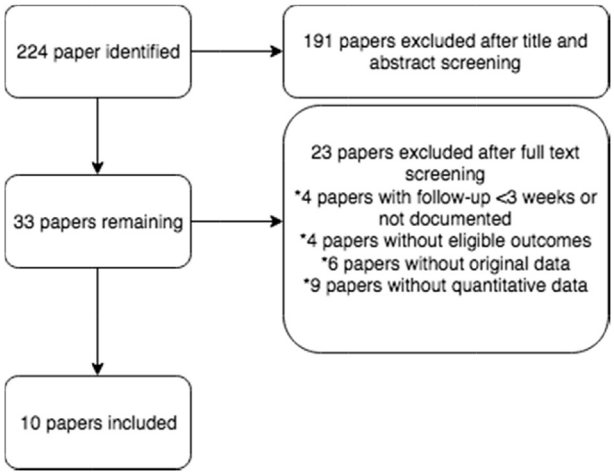

Fig. 1. Flowchart depicting the study selection process.

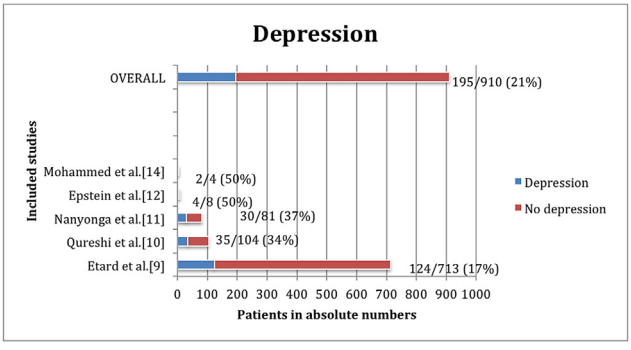

Fig. 2. Frequency of depression per individual study, and pooled analysis of data. For interval between discharge and assessment see Table 1.