LETTER

Temporary neurocognitive impairment with Ebola virus

INTRODUCTION
As of April 2016, the WHO reported a total of 28,616 Ebola virus disease (EVD) cases worldwide. This epidemic has the highest record of survivors who are now facing their challenges, including long-term sequelae. We present two patients with EVD with a complete neurocognitive recovery after impairment.

CASE REPORT
Two EVD cases were admitted to the National Institute for Infectious Diseases ‘Lazzaro Spallanzani’ in Rome. The first patient, a 50-year-old male physician, experienced EVD symptoms on 20 November 2014 and was medically evacuated from Sierra Leone, where he contracted the infection. At diagnosis, Ebola virus (EBOV) load was 6.8 log_{10} copies/mL. He had severe gastrointestinal symptoms, followed by an altered level of consciousness since day 10 of EVD for 5 days. An adult respiratory distress syndrome, which required mechanical ventilation, and a Plasmodium vivax coinfection were also diagnosed a few days later. At intensive care unit discharge, a clinically evident mild neurocognitive impairment, also reported by the patient, was observed for a further 5 days. He was discharged from the hospital on day 38.

The second case, a 36-year-old male nurse, was admitted to the hospital on day 2 of EVD symptoms onset. EBOV load was 7.70 log_{10} copies/mL. His clinical history was complicated by an acute pericarditis and mild cognitive deficits were reported by physicians on day 3 for the next 48 hours. He was discharged on day 28. No bacterial infections or bleeding disorders were observed. Both patients were treated with fluids, empiric antibiotic therapy and antivirals (favipiravir and a mixture of EBOV monoclonal antibodies).

A neuropsychological examination was performed to deeply investigate the clinical suspicion of neurocognitive impairment. The evaluation was repeated at follow-up. Neurological examination of both patients was normal at baseline and follow-up neurocognitive assessment. Tests were selected to be sensitive to a comprehensive range of cognitive domains: mental flexibility, attention and speed of mental processing, memory, visuospatial and constructional abilities and fine motor functioning. The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI-II) were also performed. The two patients were evaluated at day 30 of EVD onset and day 62 from discharge, and at day 12 of EVD onset and day 138 from discharge, respectively. At the time of baseline and follow-up neurocognitive assessments, the two patients were afibrile; no vomiting or diarrhoea was present; haemoglobin values were higher than 12 g/dL; haematocrit, coagulation, electrolytes, glucose, renal and liver function were in normal range in both patients; all alterations previously presented were normalised. At baseline, EBOV load was undetectable (lower than 3.0 log_{10} copies/mL) in plasma, respiratory swabs, stool and sweat, but still detectable in urine (3.1 log_{10} copies/mL) in both patients. At follow-up, EBOV load was only assessed in the semen and it was still detectable only in the first patient. Lumbar puncture and brain imaging were not performed due to safety concerns. No drugs apart from intravenous hydration at baseline were administered at neurocognitive assessment.

Baseline evaluation of both patients showed normal results in tasks involving mental flexibility, attention and speed of mental processing, compared to participants’ level matched for sex, age and education. Conversely, memory tasks (Rey Auditory Verbal Learning Test and Rey Complex Figure-delayed) showed mild deficits regarding learning and delayed recall (table 1). BAI scores showed a normal level of anxiety. In the first patient,

Table 1 Baseline and follow-up neuropsychological evaluation in the two Italian patients with EVD

<table>
<thead>
<tr>
<th>Neuropsychological test battery</th>
<th>First patient*</th>
<th>Second patient†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 December 2014</td>
<td>5 March 2015</td>
</tr>
<tr>
<td>Attention and speed of mental processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail making test A (s)</td>
<td>43&quot;</td>
<td>33&quot;</td>
</tr>
<tr>
<td>WASI-R digit span (forward+backward)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>WASI-R digit symbol</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail making test B (s)</td>
<td>104&quot;</td>
<td>64&quot;</td>
</tr>
<tr>
<td>Stroop colour-word (s)</td>
<td>56&quot;</td>
<td>46&quot;</td>
</tr>
<tr>
<td>Controlled oral word (FAS)</td>
<td>33.70</td>
<td>39.70</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey auditory verbal learning (total)</td>
<td>33.40</td>
<td>50.7</td>
</tr>
<tr>
<td>Rey auditory verbal learning (after 15’)</td>
<td>6.30</td>
<td>12.5</td>
</tr>
<tr>
<td>Rey complex figure (delayed)</td>
<td>15</td>
<td>67</td>
</tr>
<tr>
<td>Visuospatial and constructional abilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey complex figure (copy)</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>Self-report anxiety and depression questionnaires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Anxiety Inventory (BAI)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Beck Depression Inventory total score (BDI-II)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>BDI-II somatic-affective factor</td>
<td>85</td>
<td>20</td>
</tr>
<tr>
<td>BDI-II cognitive factor</td>
<td>70</td>
<td>50</td>
</tr>
</tbody>
</table>

The significance of * is seconds
Normal values for each test are reported between brackets. Impaired values (bold) were defined if the performance at each test was one SD lower than the mean value compared to a normal population matched for age, sex and education level or if it was below a cut-off derived from the literature. WASI-R, Wechsler Adult Intelligence Scale - Revised.

*Eighteen years of education.
†Thirteen years of education.
the presence of mild depressive symptoms, in the somatic-affective factor only, but not in the cognitive factor. However, the second patient did not present any symptoms of depression. At follow-up, a full recovery of all neuropsychological functions was observed for both patients, as compared to the baseline. Cognitive performance improved in memory tasks but notably in all domains, showing a performance higher than that observed in the previous tests, suggesting that during the acute phase of the infection all domains were impaired compared to usual performances, although they still resided within normal ranges (table 1). BAI and BDI-II scores did not suggest any sign of depression and anxiety. No psychiatric drugs or psychological support were needed for the two patients. The patients were discharged when repeated EBOV reverse-transcription-PCR (RT-PCR) of all body fluid samples apart from the semen was negative. Our patients survived to EVD and did not present any residual deficit after discharge.

**DISCUSSION**

Long-term sequelae are reported among EVD survivors. Recently, at the 2016 American Academy of Neurology Annual Meeting, Lauren Bowen referred to long-lasting neurological sequelae after EBOV infection, including weakness, headache, memory loss, depressed mood, muscle pain, tremors, abnormal eye movements and irregular reflexes. No EVD case reporting neurocognitive impairment during the acute phase of the infection has been published. During the early EVD phase, the two reported cases showed a mild reactive deficit in memory tasks, which quickly disappeared during follow-up. They had no permanent cognitive disorders and they fully recovered. EVD-associated symptoms were not present at baseline and follow-up and were unlike to have directly influenced the neurocognitive performance. No neurological imaging was performed, considering the need to minimise EBOV exposure risks in the presence of mild deficits.

Patients with EVD usually experience adjustment disorders, emotions and anxiety related to a life-threatening disease and to the strict isolation measures required for its management. All these factors are likely to have affected the neurocognitive reduced performances. Differently from acute adjustment disorders, which cause anxiety and psychological distress responses, the two patients showed specific impairments of memory abilities. A direct link between EBOV infection and pathogenetic brain damage has not yet been reported. However, it is known that EBOV can escape the host immune-surveillance and cause encephalitis. Recently, EBOV was detected in the cerebrospinal fluid of a patient with severe encephalopathy during EVD, suggesting a direct involvement of the central nervous system. Furthermore, histological lesions of choriomeningoencephalitis with strong EBOV antigen staining were found in an EBOV infected rhesus macaque female with apparent recovery and delayed time of death. These observations suggest that EBOV may be implicated in the acute involvement of the central nervous system by direct or indirect mechanisms.

In the two reported cases, the early access to therapies is likely to have contributed to the favourable outcome. Neurological and neuropsychological aspects should be considered in a comprehensive plan to emerging infectious diseases. Further prospective studies in larger cohorts are needed to understand how EBOV may affect the brain in the acute phase of the infection, as well as in the long term.

Emanuele Nicastri,1 Pietro Balestra,1 Martina Ricottini,2 Nicola Petrosillo,2 Antonio Di Carlo,2 Maria Rosaria Capobianchi,2 Maria Letizia Giancola,1 Giuseppe Ippolito,3 the INMI’s Ebola Team

1Clinical Department, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’, IRCCS, Rome, Italy
2Diagnostic Department, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’, IRCCS, Rome, Italy
3Scientific Direction, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’, IRCCS, Rome, Italy

**Correspondence to** Dr Emanuele Nicastri, Clinical Department, National Institute for Infectious Diseases—INMi—Lazzaro Spallanzani IRCCS, Via Portuense 292, Rome 00149, Italy; emanuele.nicastri@inmi.it

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Collaborators Members of the INMI’s Ebola Team (to be listed in PubMed as collaborators). IDs specialists: Nicola Petrosillo, Emanuele Nicastri, Nazario Bevilacqua, Evangelo Boumis, Pierangelo Chinello, Stefania Cicali, Angela Cordolongo, Vincenzo Galati, Andrea Mariano, Silvia Rosati, Fabrizio Taglietti, Laura Vincenzi; Intensive care physicians: Mario Antonini, Ilaria Canavella, Gabriele Garotto, Luisa Marchioni, Micaela Maritti; Pathologists: Pietro Balestra and Martina Ricottini; Radiologist: Elsa Busi Rizzi; Virology and Microbiology Laboratory: Maria Rosaria Capobianchi, Antonio di Carlo, Concetta Castilletti, Licia Bordi, Eleonora Lalle, Silvia Meschi, Daniele Lapa, Patrizia Marsella, Francesca Colavita, Laura Vitolo; Radiology Technicians: Maurizio Morea; Drivers’ biocontainment ambulance: Gaetano Battisti, Marco Liguori; Members of the INMI Crisis unit: Nicola Petrosillo, Emanuele Nicastri, Francesco Nicola Lauria, Vincenzo Puro, Mario Antonini, Antonio Russo, Maria Rosaria Capobianchi, Antonio Di Carlo, Paolo D’Aprile, Silvia Petriccchia, Evangelo Boumis, Marco Gentile, Damiano Travaglini, Silvia Pittalis, Lorena Martin, Concetta Castilletti, Francesco Maria Fusco, Simone Lanini, Andrea Antonini, Marina Cerimele, Giuseppe Ippolito and Marta Branca.

**Contributors** EN has been involved in the study concept, manuscript writing and clinical assistance. PB has been involved in the study design and in the neuropsychological test administration. MR has been involved in the neuropsychological tests analysis and interpretation. NP has been involved in the clinical assistance and in the manuscript revision. ADC has been involved in the study concept and in the virological test performance. MRC has been involved in the virological test performance, data analysis and interpretation. MLG has been involved in the manuscript drafting and revision. And GI has been involved in the critical revision of the manuscript for important intellectual content and in the study supervision.

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Emanuele Nicastri, Pietro Balestra, Martina Ricottini, Nicola Petrosillo, Antonino Di Caro, Maria Rosaria Capobianchi, Maria Letizia Giancola and Giuseppe Ippolito

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