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Single Case

Severe Neurological Involvement in an Adult with Shiga Toxin-Producing *Escherichia coli*-Hemolytic Uremic Syndrome Treated with Eculizumab

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Keywords
Shiga toxin · Hemolytic uremic syndrome · Neurological complications · Magnetic resonance imaging · Eculizumab

Abstract
A 68-year-old man with a medical history of hypertension was admitted to the emergency department for diffuse abdominal pain preceded by bloody diarrhea. Upon admission, neurological examination was normal, but he suddenly developed a left-sided hemiparesis. After a normal brain computed tomography, intravenous thrombolysis was administered for a suspicion of ischemic stroke. In the first laboratory investigations, hemoglobin was 16.9 g/dL, platelets 121 × 10^9/L (150–450), and serum creatinine 1.17 mg/dL. By the second hospital day, the platelet level dropped to 79 × 10^9/L, with haptoglobin at 0.12 g/L, 3% schistocytes, and normal ADAMTS13 activity (57%). Serum creatinine increased to 1.84 mg/dL with oliguria. The suspicion of thrombotic microangiopathy was supported by the identification of Shiga toxin genes *stx*1 and *stx*2 on a rectal swab and the isolation of an *eae*A-negative Shiga toxin-producing *E. coli* O113:H4. The patient presented a generalized tonic-clonic seizure, and orotracheal intubation was required for decreased consciousness. Plasma exchange therapy was started, and eculizumab was given 6 days after symptoms onset. Brain magnetic resonance

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imaging (MRI) on day 13 showed symmetric hyperintensities within basal ganglia that disappeared on a second MRI on day 37. At 2-month follow-up, the patient had made a complete neurological and renal recovery and eculizumab therapy was stopped.

Introduction

Shiga toxin-producing *Escherichia coli*-hemolytic uremic syndrome (STEC-HUS) is a foodborne disease that mainly affects children and causes acute kidney injury, gastrointestinal lesions, and central nervous system (CNS) manifestations [1]. Symptoms of CNS involvement include altered mental status, seizures, coma, stroke with abnormal signal intensities on brain magnetic resonance imaging (MRI) sequences/weightings in the basal ganglia, thalami, and brainstem [2].

The occurrence of STEC-HUS-related neurological symptoms varies widely and has been reported in up to 90% of adult patients affected by an outbreak of STEC-HUS caused by the Shiga toxin-producing enteroaggregative *E. coli* O104:H4 in Northern Germany in 2011 [3–6]. Despite the higher risk of death associated with severe CNS involvement in STEC-HUS, the appropriate treatment remains ill-defined. Experimental data showed that Shiga toxin directly activates complement system and case series suggested that complement inhibition with eculizumab may be beneficial in patients with STEC-HUS complicated by CNS involvement [7–11]. However, such benefit was not confirmed among patients treated during the 2011 outbreak of *E. coli* O104:H4 and whether eculizumab should be used in patients with STEC-HUS and severe CNS symptoms still remains debated [12].

Here, we present a case of reversible neurological involvement following STEC-HUS in an immunocompetent adult treated by eculizumab. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528893).

Case Report

A 68-year-old man with a past history of recent but controlled hypertension and mild dyslipidemia was admitted to the emergency department (ED) and thereafter to the intensive care unit for diffuse abdominal pain. Symptoms had started the day before with bloody diarrhea. Upon admission, vital signs showed a temperature of 36.2°C, heart rate 97/min, respiratory rate 18/min, blood pressure 147/106 mm Hg, and pulse oxygen saturation 98% on ambient air. While the neurological examination was normal on ED admission, the patient suddenly developed a left-sided hemiparesis associated with facial nerve palsy. The brain computed tomography with contrast failed to reveal any lesion. As acute ischemic stroke was clinically suspected, intravenous thrombolysis using alteplase (0.9 mg/kg) was performed in the absence of contra-indications on the computed tomography scanner. The first laboratory investigations revealed hemoglobin 16.9 g/dL (13.3–16.7), platelets 121 × 10^9/L (150–450), BUN 36 mg/dL (15–50), creatinine 1.17 mg/dL (0.60–1.30), lactate dehydrogenase 432 IU/L (<250), CRP 29.9 mg/dL (<5.0). Urinalysis showed a bland sediment and non-nephrotic proteinuria (urine protein-to-creatinine ratio, 2.5 g/g). On the second hospital day, the patient was alert and orientated, but with a relative bradypsychia. The electroencephalogram showed diffuse slowing (8 Hz) without epileptic changes. The

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platelet level had dropped to 79 × 10^9/L, rising the suspicion of thrombotic microangiopathy supported by the history of bloody diarrhea. Further laboratory investigations confirmed decreased haptoglobin level (0.12 g/L, normal 0.3–2 g/L), the presence of schistocytes (3%), normal coagulation tests and direct Coombs, and normal ADAMTS13 activity (57%). Multiplex polymerase chain reaction test (BioFire FilmArray® Gastrointestinal Panel, BioFire Diagnostics, LLC, USA; bioMérieux, France) performed on a rectal swab was positive for Shiga toxin genes *stx*1 and *stx*2, leading to the diagnosis of STEC-HUS. The isolated strain was characterized by Illumina-based next-generation sequencing as STEC O113:H4, *stx*1c- and *stx*2b-positive, intimin gene (*eae*A)-negative, and enterohaemolysin gene (*ehx*A)-positive (BioNumerics v.8.1, Applied Maths, bioMérieux, Belgium). Given the severity of the clinical presentation, genetic testing was performed using next-generation sequencing and multiplex ligation-dependent probe amplification, and found no pathogenic variant in a panel of complement genes (*CFH*, *CFI*, *CD46*, *C3*, *CFB*, and *CFHR1-5*).

A first session of plasma exchange (volume exchanged 3,800 mL, mixed substitution with plasma and albumin solution) was performed. On day 3, suddenly, the patient presented a generalized tonic-clonic seizure controlled by the administration of 4 mg lorazepam and 1,000 mg levetiracetam. Orotracheal intubation was required for decreased consciousness. By the third hospital day, urine output progressively decreased with serum creatinine rising to 1.84 mg/dL. After a second session of plasma exchange, the patient was transferred to the intensive care unit of a tertiary university hospital to discuss the indication of eculizumab therapy. The patient was mechanically ventilated with minimal sedation and was only poorly reactive to painful stimulation (Glasgow Coma Scale score was E1V1M4). Repeated EEG recording showed only diffuse slowing of brain waves (5–6 Hz). In total, three sessions of plasma exchange were performed. Eculizumab (900 mg) was initiated 6 days after the onset of neurological symptoms at a dose of 900 mg weekly, for 4 weeks, followed by maintenance treatment with eculizumab 1,200 mg every other week. Before the administration of eculizumab, the patient was vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* (groups A, B, and C), and *Haemophilus influenzae*. He also received antibioprophylaxis with azithromycin for the duration of eculizumab therapy. Effective complement inhibition was achieved under eculizumab (CH50 activity 3%). The evolution of platelet count, lactate dehydrogenase, and kidney function is illustrated in Figure 1. Renal replacement therapy was never needed. The precise assessment of neurological recovery was impaired by the use of sedative drugs during mechanical ventilation that was prolonged until day 14 as the patient had early acquired *Serratia* pneumonia and presented also some degree of laryngeal oedema. After extubation, he was found apathetic and with extrapyramidal signs in the upper limbs. He presented reduced attention and was not able to follow a conversation responding with a limited number of words. A brain MRI was therefore performed on day 13 which revealed hyperintense signal changes within supra-tentorial gray nuclei (Fig. 2a, b) and the infra-tentorial dentate nuclei (not shown) on the T2-weighted views. The absence of cytotoxic oedema on the diffusion-weighted imaging (not shown), together with the absence of arterial territoriality and the strict left-right symmetry of the lesions in both supra- and infra-tentorial spaces, ruled out the hypothesis of an ischemic injury. The patient was transferred to a rehabilitation unit on day 28 with a favorable subsequent functional outcome.

On day 37, a follow-up brain MRI showed normalized brain status with complete subsidence of abnormal signal intensity changes (Fig. 2c, d) when compared to initial MR examination. Eculizumab therapy was definitely stopped after 2 months. At this time, the patient had made a complete cognitive and functional recovery.

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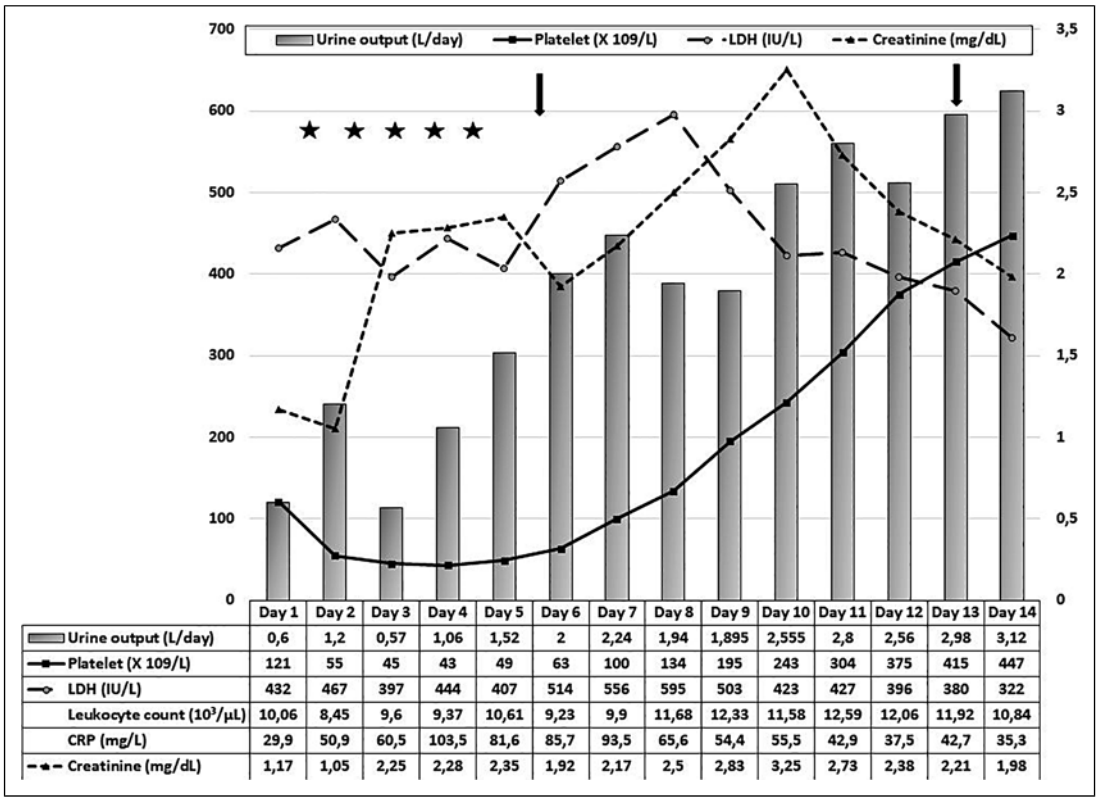

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Urine output (L/day)	0,6	1,2	0,57	1,06	1,52	2	2,24	1,94	1,895	2,555	2,8	2,56	2,98	3,12
Platelet (X 109/L)	121	55	45	43	49	63	100	134	195	243	304	375	415	447
LDH (IU/L)	432	467	397	444	407	514	556	595	503	423	427	396	380	322
Leukocyte count (10^3/µL)	10,06	8,45	9,6	9,37	10,61	9,23	9,9	11,68	12,33	11,58	12,59	12,06	11,92	10,84
CRP (mg/L)	29,9	50,9	60,5	103,5	81,6	85,7	93,5	65,6	54,4	55,5	42,9	37,5	42,7	35,3
Creatinine (mg/dL)	1,17	1,05	2,25	2,28	2,35	1,92	2,17	2,5	2,83	3,25	2,73	2,38	2,21	1,98

Fig. 1. Evolution of laboratory data and renal function from hospital admission. Legend: ↓, eculizumab administration; *, plasma exchange.

Discussion

Our patient presented a STEC-HUS with a complete recovery of the initial CNS involvement. The isolated strain was an *eae*A-negative STEC O113:H4. This serotype has been previously isolated from foods of bovine origin and has been implicated in human illness [13–15]. Yet, to the best of our knowledge, reports of HUS cases associated with O113:H4 are lacking. During a major STEC outbreak in Northern Germany in 2011, 855 patients developed HUS and 90% were adults. In comparison with previous STEC-HUS outbreaks affecting mainly children and involving the serotype O157:H7, the German outbreak was related to the serotype O104:H4 and was characterized by a high incidence of neurological complications [4–6]. The incidence of STEC-related neurological complications was investigated in a cohort of 217 patients, of whom 104 (48%) presented with neurological symptoms [4]. The prominent initial neurological symptom was a disturbance of cognitive functions, including disorientation, reduced attention, restlessness, anxiety, and amnestic deficits. Epileptic seizures occurred in 8.7% of the patients, but this incidence significantly increased (34.6%) within the first week. In 70 patients who were investigated with brain MRI, the main typical pattern was the presence of symmetrical hyperintensities on T2-weighted imaging in the region of the nucleus of the sixth cranial nerve and the lateral thalamus, without evidence of hemorrhages or ischemic infarcts. Of note, a significant number (36%) of patients had normal brain MRI despite serious cognitive dysfunction. There was no specific radiological finding for the O104:H4 serotype, and lesions in adults or children appeared rather similar. The characteristics of the MRI findings (symmetric and rapidly reversible hyperintensities,

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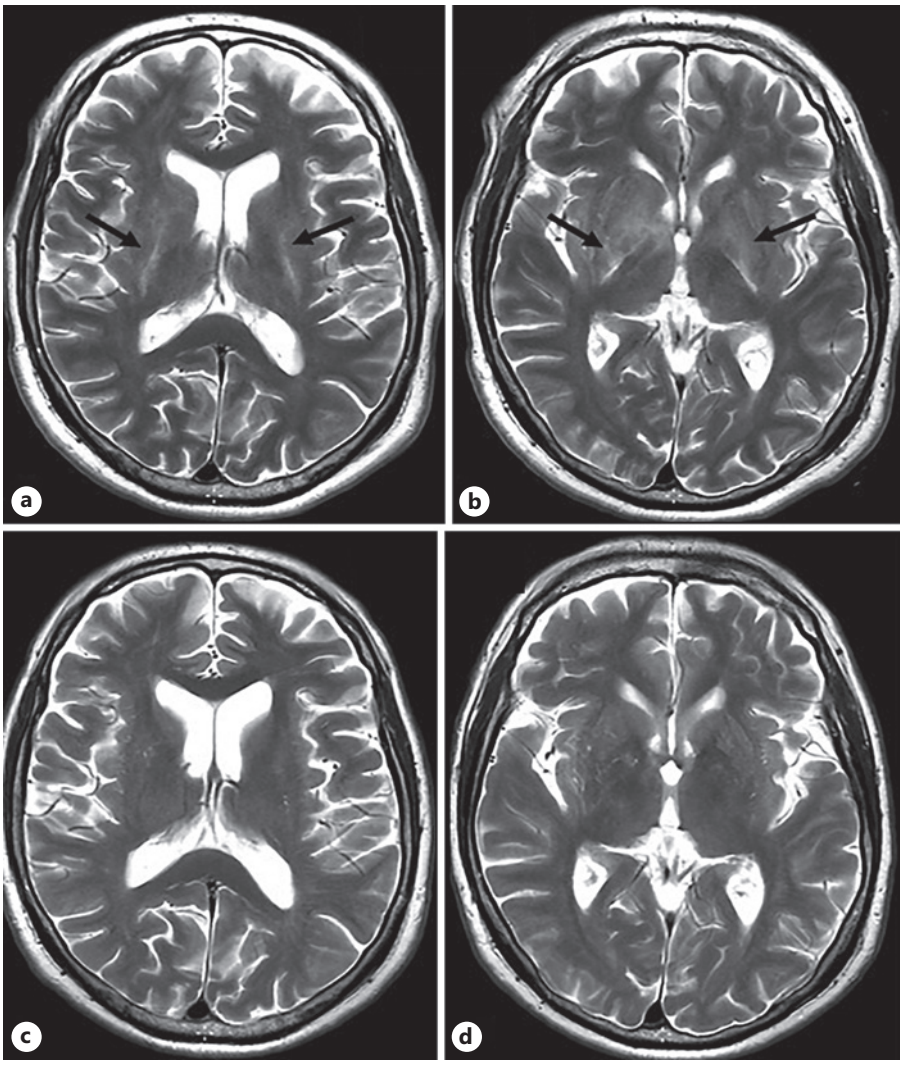

Fig. 2. Magnetic resonance (MR) work-up: four T2-weighted axial transverse views. Upper row: views from examination dated June 13 (day 13); lower row: similar slice locations in July 7 (day 37). **a** Symmetrical and linear abnormally increased signal intensity along the medial border of the globi pallidi (arrows). **b** Slightly more caudal slice than previous view revealing symmetrical hyperintense signal changes (arrows) involving the whole lenticular nuclei (globi pallidi + putamina). **c**, **d** Electronically co-registered views allowing comparison between slices in strictly similar location (**a** with **c** and to **b** with **d**) demonstrated complete subsidence of the abnormal signal intensities 3 weeks later.

absence of microthrombi or hemorrhagic lesions) seemed in favor of a toxic or inflammatory (rather than ischemic) mechanism of injury. Another series of 57 patients from the same outbreak highlighted the pattern of symmetric hyperintensities in bilateral thalamus bilateral pons, centrum semiovale, and splenium of corpus callosum [6]. The EEG changes were aspecific, ranging from normal α frequency to severe general slowing with 2–3/s δ waves in frontal derivations as frequently seen in metabolic encephalopathy. There was a poor correlation with clinical findings [5].

It could be hypothesized that the Shiga toxin was directly responsible for neurological complications. Shiga toxin can bind to the globotriaosylceramide (Gb3) receptor on the surface of the endothelial cells; in addition, Gb3 receptor expression has been shown on

neurons in a mouse model and also on neurons and endothelial cells in human autopsy brains [16]. On the other hand, there is also in vitro documentation that complement activation may occur in STEC-HUS [7, 17–20]. Shiga toxin directly activates complement via the alternative pathway through its binding to complement factor H and complement factor H-related protein [21, 22]. Albeit indirect and limited, these data suggest that complement inhibition may potentially be helpful for the treatment of severe STEC-HUS with life-threatening complications. Eculizumab is a monoclonal antibody that binds to complement protein C5, and is successfully used in the treatment of complement-mediated primary atypical HUS [7]. The potential benefit of eculizumab in STEC-HUS has not been established to date and remains a matter of debate and ongoing research. Based on the dramatic effectiveness of eculizumab in atypical HUS, and on evidence showing complement activation during STEC-HUS, complement blockade has been attempted and reported in some cases and small series [8–11]. In a first report including 3 young patients with severe STEC-HUS (i.e., neurological involvement), administration of eculizumab was rapidly followed by a dramatic resolution of symptoms, suggesting potential benefit of therapeutic complement blockade [8]. The unexpected severity of the disease during the German outbreak prompted an urgent quest for therapeutic options, and the use of eculizumab was suggested in severely affected patients, including those with neurological involvement. A retrospective, case-control study during the German outbreak of STEC-HUS failed to demonstrate any benefit of complement blockade in the 67 patients treated with eculizumab. However, the study had major limitations, including the non-randomized design, differences in disease severity at baseline, and delayed initiation of eculizumab, administered more than 10 days after presentation, precluding any formal conclusion [12]. As this represents a major gap in the current knowledge, two randomized, double-blinded, placebo-controlled clinical trials are currently investigating the efficacy and safety of complement inhibition in STEC-HUS (NCT02205541, ISRCTN89553116). Interestingly, a prospective, non-randomized study also conducted during the German outbreak showed that immunoadsorption was associated with improvement in composite neurological symptom scores in 12 adult patients with STEC-HUS and severe neurological symptoms unresponsive to plasma exchange and eculizumab [23]. These preliminary data suggested that antibodies may be involved in the pathogenesis of severe neurological symptoms in STEC-HUS, calling for further evaluation [23].

Statement of Ethics

A formal approval for a single case report was waived by the local Institutional Review Board of the Cliniques Universitaires St-Local, Brussels (Ref EC322/2022). A written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that they have no relevant financial interests.

Author Contributions

P.V. and H.G. drafted the first version of the paper, T.D. supervised the radiological investigations, L.G. and C.C. were directly involved in the clinical management, J.M. was the consultant nephrologist, A.V. and F.C. performed the microbiological investigations, P.H. was the medical supervisor and approved the final version of the manuscript.

Data Availability Statement

All data that support the findings of this study are included in this article and its online supplementary material. The genomic assembly of the *E. coli* O113:H4 strain is available online in the EnteroBase *Escherichia*/*Shigella* database (EnteroBase barcode: ESC_AB4978AA). Further inquiries can be directed to the corresponding author.

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