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# Eculizumab in Typical Hemolytic Uremic Syndrome (HUS) With Neurological Involvement

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**Abstract:** In typical hemolytic uremic syndrome (HUS) approximately 25% of patients show central nervous system (CNS) involvement often leading to serious long-term disabilities. We used the C5-complement inhibitor Eculizumab as rescue therapy.

From 2011 to 2014, 11 children (median age 22 months, range 11–175) with enterohemorrhagic *Escherichia coli*-positive HUS requiring dialysis who had seizures (11/11) and/or were in a stupor or coma (10/11) were treated with Eculizumab. Two patients enrolled on the Safety and Efficacy Study of Eculizumab in Shiga-Toxin Producing *E coli* Hemolytic-Uremic Syndrome (STEC-HUS) each received 6 doses of Eculizumab, 3 patients 2 doses, and 6 patients 1 dose. Laboratory diagnostics of blood samples and magnetic resonance imaging (MRI) were performed as per center practice. Data were analyzed retrospectively.

Cranial MRI was abnormal in 8 of 10 patients with findings in the basal ganglia and/or white matter. A 2-year-old boy with severe cardiac involvement and status epilepticus needed repeated cardio-pulmonary resuscitation and extracorporeal membrane oxygenation. He died 8 days after start of Eculizumab treatment. Two patients with hemorrhagic colitis and repeated seizures required artificial ventilation for 6 and 16 days, respectively. At the time of discharge, 1 patient showed severe neurological impairment and 1 mild neurological impairment. The 8 surviving patients experienced no further seizures after the first dose of Eculizumab. Three patients showed mild neurological impairment at discharge, whilst the remaining 5 showed no impairment. The platelets normalized 4 days (median) after the first dose of Eculizumab (range 0–20 days). The mean duration of dialysis after the first dose of Eculizumab was  $14.1 \pm 6.1$  days.

In children with typical HUS and CNS involvement early use of Eculizumab appears to improve neurological outcome. In severe HUS cases which progress rapidly with multiple organ involvement, late treatment with Eculizumab seems to show less benefit. We speculate that prophylactic Eculizumab therapy before development of neurological symptoms could be advantageous.

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**Abbreviations:** ADC = apparent diffusion coefficient, CNS = central nervous system, HUS = hemolytic uremic syndrome, MRI = magnetic resonance imaging, STEC-HUS = Shiga-toxin producing *Escherichia coli* hemolytic-uremic syndrome.

## INTRODUCTION

Shiga toxin-positive haemolytic-uremic syndrome (HUS) is the most frequent cause of acute renal failure in children.<sup>1</sup> It is mainly caused by *Escherichia coli* serotype O157:H7. HUS was first described by Gasser et al in 1955.<sup>2</sup> The primary clinical features are thrombocytopenia, hemolysis with fragmentocytes, and renal failure.<sup>3</sup> The primary pathophysiologic mechanism in HUS is endothelial damage caused by Shiga toxin followed by activation of the complement cascade,<sup>3–6</sup> leading to thrombotic microangiopathy mainly in the kidney. Other organs can be affected by microvascular and cellular damage. Most often, kidney damage is not permanent and renal function recovers. As well as renal failure, cerebral involvement plays an important role in HUS pathology.<sup>7–10</sup> Unfortunately, until now, there has been no adequate routine treatment for neurologic symptoms including seizures, paresis, coma, and visual disturbance,<sup>11–14</sup> and neurological sequels are frequent.<sup>13</sup> Plasmapheresis has been used without significant success in improving neurological outcome.<sup>13</sup>

In atypical HUS, a disorder that differs from typical HUS, abnormalities of complement-regulating proteins have been demonstrated and treatment with the monoclonal C5 inhibitor Eculizumab is highly effective.<sup>15</sup> Similarly, in many cases of typical HUS, activation of complement by Shiga toxin and the binding of factor H is found.<sup>14</sup> In 3 single cases Eculizumab has been used very successfully as rescue therapy for neurological involvement of typical HUS.<sup>16</sup>

In this study, we present the results of 11 children with enterohemorrhagic *E coli* (EHEC)-positive HUS with neurological involvement treated with Eculizumab.

## METHODS

Eleven children (median age 22 months, range 11–175), 6 female and 5 male with EHEC-positive HUS with neurological symptoms, were treated with Eculizumab between 2011 and 2014 at our institution (Table 1). None of the patients were treated with plasmapheresis.

All patients were assessed neurologically by the same pediatric neurologist (author H.H.). As soon as a patient developed seizures, and if the patient was already hospitalized in our clinic, Eculizumab was administered within 4 hours. If the first seizures occurred elsewhere, Eculizumab could not be given before transfer to our hospital. Two patients (patient nos. 1 and 2) were participants of the Safety and Efficacy Study of Eculizumab in Shiga-Toxin Producing *Escherichia Coli* Hemolytic-Uremic Syndrome (STEC-HUS) (NCT01410916) and

TABLE 1. Patient Characteristics

Patient No.	Age (mo)	Sex	Eculizumab (No. of Doses)	Dialysis (Days After Eculizumab Start)		Thrombopenia (Days After Eculizumab Start)		Neurological symptoms and signs			MRI
				Initial	After 6–12 months	Initial	After 6–12 months	Initial	At discharge	Follow-up	
1	175	F	6	4	7	1 GTCS	+	+	Normal		Late: normal
2	120	F	6	8	4	1 focal seizure, hemiparesis	+	None	WM		Late: normal
3	28	M	1	[†]	[†]	SE	[†]	[†]	BG, thalami		[†]
4	34	F	2	23	20	Repeated GTCS, hemiparesis	++	None	BG, thalami		Early: progress
5	13	F	2	16	8	1 GTCS	None	None	%		%
6	17	M	2	20	19	SE	+++	+++	WM, BG, thalami		Early: WM improved; BG & thalami progress
7	14	M	1	15	0	1 GTCS	+	None	BG, thalami		%
8	11	F	1	13	3	1 GTCS	None	None	Normal		%
9	33	F	1	7	4	1 GTCS	None	None	Cortical, thalami		Early: progress
10	21	M	1	16	4	1 GTCS	None	None	WM, thalami		Early: improved
11	22	M	1	19	2	1 GTCS	None	None	WM		Early: improved

All patients presented with seizures (GTCS = generalized tonic clonic convulsion; SE = status epilepticus). Neurological symptoms and signs at discharge and on follow-up were graded as none, + (only subjective deficits), ++ (clinical signs of mild neurological dysfunction such as difficulties swallowing), or +++ (clinical signs of severe neurological dysfunction, eg, hemiparesis). If the initial MRI was abnormal, the localization of signal changes is given (BG = basal ganglia; WM = white matter). Follow-up MRIs were performed within 2 weeks during the acute illness (early) in 5 patients and in 2 patients after 6 and 15 months (late) to rule out long-term sequelae.

were therefore treated with 6 doses of Eculizumab according to the study protocol (Table 1). Data for these patients have in part already been presented in a retrospective analysis of the 2011 German STEC-HUS epidemic.<sup>17</sup> For the other patients, Eculizumab was administered weekly as long as neurological symptoms were evident and HUS was active. Therefore, 3 patients received 2 doses each and 6 children received 1 dose each of Eculizumab. Dosing was given according to the pediatric prescribing information for atypical HUS as approved by the Federal Drug Agency.<sup>18</sup>

As Eculizumab therapy was used off-label, informed consent was given after a thorough discussion with the intensive care physicians, the pediatric nephrologist, and the patient's family. According to the German law, each case was an individual "Heilversuch" (therapeutic trial) and thus permission from the local ethics committee was unnecessary for those patients not taking part in the STEC-HUS-Eculizumab trial. The drug was paid for by the university hospital for those not participating in the STEC-HUS study; medication for those enrolled in the study was provided by Alexion Pharmaceuticals.

Laboratory diagnostics of blood samples and magnetic resonance imaging (MRI) were performed as a matter of routine.

Data were evaluated retrospectively from Hannover Medical School patient files. All data were tested for normal distribution by the Kolmogorov–Smirnov test. Where values were normally distributed, mean and standard deviation are reported; otherwise, median and range were calculated.

## RESULTS

### Neurology

All 11 patients experienced seizures. Ten out of 11 patients showed disturbance of consciousness, with somnolence in 8 and stupor in 2 (Table 1). Focal neurological deficits (hemiparesis) were observed in 2 patients but were transient in both.

Five out of 11 patients required mechanical ventilation in the intensive care unit for a median of 5 days.<sup>1–16</sup> At time of discharge, 3 out of 10 surviving patients showed only subjective neurological deficits, including 1 with transient hemiparesis. One out of 10 had mild impairment with difficulties swallowing and deficits in motor coordination and 1 out of 10 severe neurological sequelae (tetraparesis and severe cognitive impairment including loss of speech) (patient no. 6) (Table 1). Six months after the acute phase of disease, this patient still showed significant neurological sequelae although neurological examination was normal for all other patients. However, 1 adolescent patient (patient no. 1) reported reduced performance regarding concentration and speed of mental processing (Table 1).

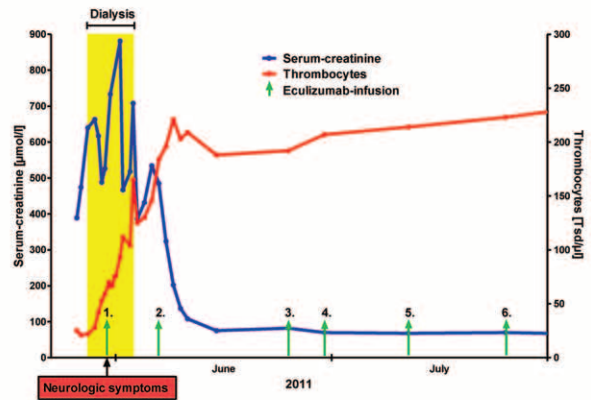
The clinical course of 3 sample patients (patient nos. 1–3) is described in Figure 1.

### MRI

Cranial MRI including diffusion weighted imaging (DWI) was performed in 10 of 11 patients within 1 day following onset of neurological symptoms (Table 1). MRI was normal in 2 of 10 patients. In 4 of 10 patients, the initial MRI showed a pattern of involvement predominantly of the white matter, but also of the basal ganglia or thalami in 2 patients. In 4 of 10 patients signal changes were detectable in the basal ganglia and/or thalami only. Due to worsening or ongoing clinical symptoms, early follow-up imaging during the phase of acute illness was performed in 5 of 10 patients within 2 weeks. Whereas white matter abnormalities resolved in 3 patients, signal changes in the basal

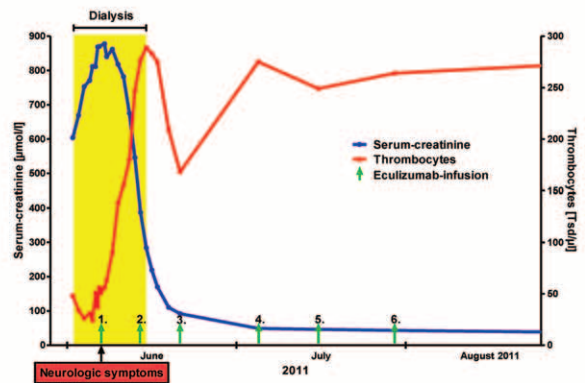
Patient No. 1

Fourteen-year-old girl with rapid cessation of seizures within one day. The patient required 8 days of hemodialysis.



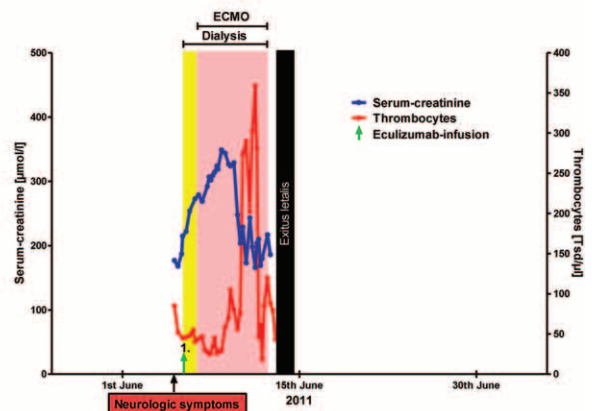
Patient No. 2

Ten-year-old girl with 14 days of dialysis. No further seizures after first dose of Eculizumab.



Patient No. 3

Two-year-old boy with persisting severe neurologic and cardiac involvement. Death after 1 week of extracorporeal membrane oxygenation therapy (ECMO) and dialysis



**FIGURE 1.** Three examples of children with Eculizumab treatment in cases of STEC-HUS with neurological involvement. Patient no. 1, 14-year-old girl with rapid cessation of seizures within 1 day. The patient required 8 days of hemodialysis. Patient no. 2, 10-year-old girl with 14 days of dialysis. No further seizures after first dose of Eculizumab. Patient no. 3, 2-year-old boy with persisting severe neurologic and cardiac involvement. Death after 1 week of extracorporeal membrane oxygenation therapy (ECMO) and dialysis.

ganglia progressed or were stable in 3 other patients. Late follow-up MRI was performed in 2 patients after 6 and 15 months respectively, which subsequently showed normal results in both. Table 1 summarizes the MRI findings in our patients. Figure 2 shows consecutive MRI findings in 1 patient (patient no. 10) before and after administration of Eculizumab.

### Laboratory

The platelets of the 10 surviving patients normalized to  $\geq 150,000/\mu\text{L}$  within a median of 4 days (range 0–20) after the first dose of Eculizumab (Table 1).

### Dialysis

Peritoneal dialysis (n=9) and hemodialysis (n=2) were started in all patients within 2 days after admission. The mean duration of dialysis after the first dose of Eculizumab was  $14.1 \pm 6.1$  days (Table 1).

### Complications

A 2-year-old boy (patient no. 3) with severe cardiac involvement who was admitted to our hospital with status epilepticus needed repeated cardio-pulmonary resuscitation with subsequent extracorporeal membrane oxygenation therapy. This patient had suffered repeated seizures before transfer to our hospital. Eculizumab was administered on the day of admission at our center and not in the primary hospital where treatment was previously given. The patient died 8 days after the start of Eculizumab treatment from cardiac failure.

Another patient (patient no. 6) with hemorrhagic colitis and severe prolonged seizures requiring medical resuscitation was on a ventilator for 6 days, required catecholamines, and showed significant neurological deficits at the time of discharge. An anus praeter was constructed in surgery. The neurological deficits only slowly improved over long-term rehabilitation and 1 year after his HUS episode his anus praeter was removed and normal gut continuity was restored.

A 2-year-old girl (patient no. 4) also developed severe hemorrhagic colitis and required an ileostomy. In addition, this patient showed cardiac failure and developed pancreatic necrosis during the course of HUS. She initially presented with convulsive status epilepticus requiring deep sedation and mechanical ventilation. At the time of discharge, she was able to walk without support and talk although neurological examination showed difficulties swallowing and deficits in motor coordination.

### Side Effects

There were no side effects from Eculizumab. All children, who had not been vaccinated against meningococci, received a quadrivalent meningococcal conjugate vaccine before first Eculizumab application and, additionally, antibiotic prophylaxis with cefotaxime or azithromycin for 2 weeks.

### Mutation Screening

Mutation screening for atypical HUS was performed in all patients. No abnormalities pathognomonic for HUS could be found in any of the children for CFH, CFI, CFB, MCP, and TBDM genes.

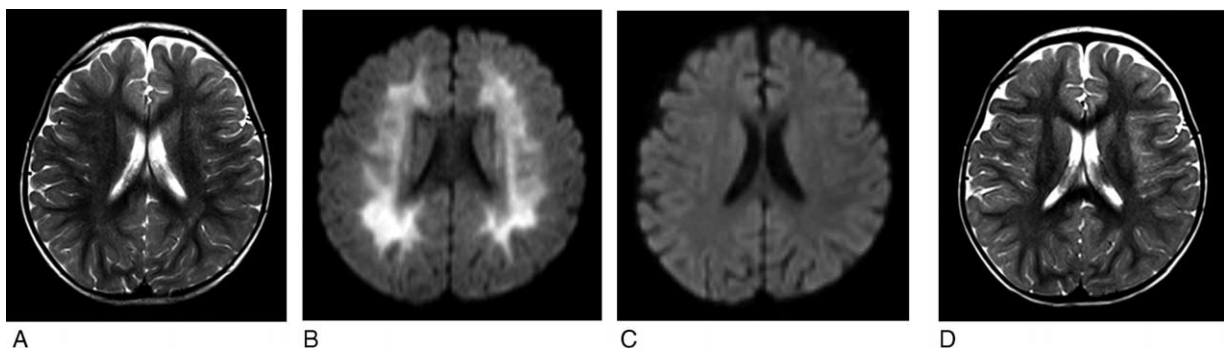
### Microbiology

Shiga toxin-producing *E coli* were cultured from the stool of 8 patients. Shiga toxin production was detected by using toxin enzyme-linked immunosorbent assay. Shiga toxin genes were detected using polymerase chain reaction (PCR). In 3 patients the pathogen was not isolated. Two out of these patients had a positive stool Shiga toxin molecular test; the third patient showed O157-specific IgM antibodies indicating recent infection with EHEC.

## DISCUSSION

In children with typical HUS and CNS involvement our retrospective analysis shows that early use of Eculizumab was associated with good neurological outcome. However, in patients with rapidly progressing HUS and multiple organ involvement, Eculizumab seems to be less beneficial.

These findings correspond to the clinical course of a case report of 3 children with Shiga toxin-associated HUS and neurological involvement treated with Eculizumab,<sup>16</sup> and the study of Gitiaux et al<sup>19</sup> which described the clinical course and MRI in 7 patients with HUS treated with Eculizumab. Similar to our findings, they described swift recovery of neurological symptoms associated with a rapid normalization of markers of disease activity in patients with primarily white matter involvement. Interestingly, 2 patients with the most pronounced reduction of the apparent diffusion coefficient (ADC), indicating cellular edema in the putamen and caudate nucleus, died. In our previous study on MRI with diffusion-weighted imaging performed early during HUS, we observed 2 patterns of cerebral involvement.<sup>20</sup> Half of the patients displayed reduced water diffusibility in the supratentorial white matter; this was



**FIGURE 2.** Results of magnetic resonance imaging (MRI) (patient no. 10). A, Initial axial diffusion-weighted imaging (DWI), B, depicted bilateral massive acute restriction in the intermediate white matter without any signal abnormalities on the axial T2-weighted image (A). Within 9 days the diffusion restriction disappeared (C) and the long-term follow-up scan showed no residual signal abnormalities (D).

associated with hyponatremia. The remaining patients showed involvement of grey matter (basal ganglia and thalami), which we speculated might reflect thrombotic microangiopathy, whereas the white matter changes might be related to the toxic effects of Shiga toxin. Two of our current patients had severely reduced ADC in the white matter only, which resolved with only minimal T2 signal changes within 9 days in 1 patient and without any residuals on late follow-up in the other. Both patients had an excellent neurological course.

Typical HUS with neurological impairment is a life-threatening disease and leads to severe long-term neurological damage and patient death.<sup>13</sup> Hitherto, no treatment of neurological complications has been available. The benefit of plasma exchange therapy has been discussed but could be neither demonstrated in a large, retrospective adult study<sup>21</sup> nor in a retrospective analysis of children.<sup>22</sup> In view of a lack of alternative therapeutic options, in single cases, a potentially life-saving intervention with Eculizumab could be justified.

The positive responses with Eculizumab could be explained by the fact that in typical HUS it has been shown that the complement is directly activated.<sup>14</sup> Hyperactivation of complement in typical HUS was demonstrated by Thurman et al.<sup>23</sup> The pathogenetic mechanisms of CNS involvement in HUS are not fully understood. Brain autopsy in deceased patients showed evidence for thrombotic microangiopathy in only 11 of 32 patients,<sup>24</sup> but intracranial hemorrhage in 21 of 32 and brain swelling in 16 of 32. Our finding that reduced ADC in the supratentorial white matter may be reversible within days is suggestive of a toxic mechanism rather than thrombotic microangiopathy, which would be expected to resolve over a longer period. This could also explain the good neurological outcome observed by Gitiaux et al in patients where white matter was the primary involvement.<sup>19</sup> We speculate that treatment with Eculizumab in patients with typical HUS and CNS involvement would not influence the early toxic effects of Shiga toxin on myelin (as diagnosed by ADC reduction in the supratentorial white matter in our patients), but may help prevent complement-mediated pathology, especially thrombotic microangiopathy. Therefore, proposing Eculizumab therapy for children with typical HUS appears to be mechanistically logical.

Our data suggest that early treatment of neurologic symptoms of HUS with Eculizumab can lead to better neurologic outcome than that observed previously using conservative therapy.<sup>13</sup> However, in cases of rapidly progressing HUS with multiple organ involvement and delayed start of Eculizumab therapy we observed unsatisfactory outcomes, including 1 death. Accordingly, it seems crucial to initiate Eculizumab treatment within hours of the first signs of neurological involvement. This is supported by the fact that a large trial in adult patients has shown no advantage of Eculizumab on neurological outcome when therapy was delayed for several days or weeks following unsuccessful treatment with plasmapheresis.<sup>21</sup>

No severe side-effects of Eculizumab could be detected, notably an absence of infections. As Eculizumab inhibits the formation of the membrane attack complex, which is an integral component of innate immunity, an increase in bacterial infections could be expected due to impaired host defense. It is well known that patients with C3 deficiencies have a high risk for bacterial, viral, and fungal infections.<sup>25</sup> However, Eculizumab does not affect C3 function, so opsonization of pathogens by C3b would still be possible. In inborn C5 deficiency, which resembles C5 inhibition by Eculizumab, no such significant infections could be shown despite meningococemia or pneumococcal infections.<sup>26</sup> In adults with paroxysmal nocturnal

hemoglobinuria long-term administration of Eculizumab was also found to be safe<sup>27</sup> without any elevated risk of infection. In typical HUS bacteremia is extremely rare,<sup>28</sup> as the infection is mainly confined to the intestinal mucosa. Systemic effects of the disease are mostly mediated by Shiga toxin during the period when the patient is recovering from intestinal infection.

Eculizumab was administered in patients with typical HUS in the large EHEC O104:H4 outbreak in Germany 2011. Retrospective analyses of this German cohort found no definite positive effect of Eculizumab on the clinical course of patients.<sup>21,29</sup> However, in the adult patients analyzed Eculizumab was not administered at the onset of either disease or neurological complications but most often after days or weeks of plasma exchange therapy. This supports our preliminary findings that late administration of Eculizumab is not beneficial. Early intervention with Eculizumab preventing initial activation of the complement system is the more reasonable alternative.

Three of the 11 patients had characteristics of the German *E coli* outbreak strain O104:H4 of 2011, including its typical resistance profile due to the production of an extended beta lactamase. This strain shows advanced adherence to intestinal epithelial cells which, it has been speculated, cause increased virulence and longer fecal shedding.<sup>30</sup> A multicenter study from the German outbreak determined a median shedding duration of 14 days in HUS patients and 34 days in non-HUS patients.<sup>31</sup> During the German outbreak, 98% of patients treated with Eculizumab received azithromycin or other antibiotics for meningococcal prophylaxis.<sup>29</sup> It is known that Eculizumab increases the risk of meningococcal infections, so all 11 patients in our retrospective analysis received prophylaxis with cefotaxime or azithromycin. The role of antibiotic administration in EHEC patients has been controversial as it may induce or aggravate HUS. Induction of toxin production in the German outbreak strain *E coli* O104:H4 could be demonstrated following exposure to ciprofloxacin but not to meropenem, azithromycin, or rifampicin. Thus, the current recommendation for meningococcal prophylaxis favors azithromycin or rifampicin.<sup>32</sup>

In conclusion, it can be speculated that in HUS cases with neurologic involvement early Eculizumab therapy could be advantageous in reducing long-term neurological sequelae. In patients with rapidly progressing HUS, prophylactic therapy before development of neurological symptoms may be considered. To confirm our findings, a prospective randomized trial is needed to compare neurological outcome with Eculizumab versus placebo treatment in children with EHEC-positive HUS. Given the number of children with this condition, such a study seems feasible.

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*L.P. and H.H. wrote the primary draft of the manuscript. T.A.-G. collected all data, did the statistical analyses, and corrected the manuscript. F.C.B. and S.S. contributed the bacteriological data and corrected the last version of the manuscript. E.B. contributed the MRI images and the corresponding evaluations and corrected the last version of the manuscript.*

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