CASE REPORT: HEMOLYTIC UREMIC SYNDROME WITH MULTIPLE ORGAN DAMAGE

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RUNNING TITLE	Hemolytic uremic syndrome with multiple organ damage
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ABSTRACT

Typical HUS is one of the most common causes of the community acquired acute kidney failure in young children. It is characterized by the microangiopathic hemolytic anemia, thrombocytopenia and renal insufficiency. The most common etiological factor is STEC infection, which primary manifests with diarrhea. Life-threatening multiple organ damage (MOD) with central nervous systems (CNS) involvement develops in some cases, and then the treatment of monoclonal antibody might be considered. A previously healthy 2 years old girl was hospitalized in Children's Clinical University Hospital with febrile temperature for 4 days, bloody diarrhea, abdominal pain and decreased diuresis followed by anuria. Laboratory data revealed leukocytosis, anemia, thrombocytopenia, serum creatinine – 365.46 mcmol/L, GFR-11.9 ml/min/1.73 m^2 by Schwartz Equation. EHEC serotype O26 was found in the feces. The diagnosis of the tHUS was established. The disease progressed. Patient had arterial hypertension, prolonged episodes of nausea, vomiting, elevated glucose level. Neurological impairment involved behavioral disturbances and left side hemiparesis. Ischemic lesions in the basal ganglia and brainstem were demonstrated by magnetic resonance imaging. According to the development of MOD with CNS involvement, the therapy of Eculizumab was started. After that patients neurological state and renal function slightly improved, however complete recovery was not made. This case shows that monoclonal antibody can be used when the tHUS presents with CNS involvement. However, in this case therapy with Eculizumab was started after 8 weeks from the onset of the disease, and that may explain why patients complete recovery was not made.

BACKGROUND

Typical HUS is one of the most common causes of the community acquired acute kidney failure in young children [1, 2]. It is characterized by the microangiopathic hemolytic anemia, thrombocytopenia and renal insufficiency. The most common etiological factor is STEC infection, which primary manifests with diarrhea [1, 3]. Life-threatening MOD develops in some cases, and approximately 25-30% of tHUS patients show central nervous systems (CNS) involvement [4, 5]. Monoclonal antibody Eculizumab could be used as a rescue treatment in these cases [5, 6].

CASE PRESENTATION

A previously healthy 2 years old girl was hospitalized in Children's Clinical University Hospital with febrile temperature for 4 days, bloody diarrhea, abdominal pain and decreased diuresis followed by anuria. Laboratory data revealed leukocytosis (WBC – 21.66x103/uL), anemia (RBC – 3.01x106/uL, HGB – 8.3 g/dL), and thrombocytopenia (PLT - 48x103/uL). Serum creatinine was 365.46 mcmol/L and GFR – 11.9 ml/min/1.73 m^2 by Schwartz Equation. Acute kidney failure was developed, and that indicated that automated peritoneal dialysis (APD) had to be started. In the next few days EHEC serotype O26 was found in the feces. The diagnosis of the typical HUS was established. But the disease progressed. Patient had general edema with pleural effusion in the both sides of the chest, thoracocentesis was done. She also had arterial hypertension (135/95 mmHg), due to which she received combined antihypertensive treatment. Girl also had prolonged episodes of nausea, vomiting, and elevated glucose level (7.90 mmol/l). She had severe problems with food intake in the proper amount, therefore she was fed through feeding tube. Neurological impairment was observed after 4 weeks of hospitalization, and it involved behavioral disturbances and also left side hemiparesis with muscle dystonia on the right side extremities. During her hospitalization patient experienced atypical seizures twice. Ischemic lesions in the basal ganglia and brainstem were shown in magnetic resonance imaging (MRI), which was done when the neurological symptoms appeared (Fig. 1A). 13 weeks later scarring process was detected in that area of brain by MRI (Fig. 1B). Laboratory data of complement showed increased C3 (2.13 g/L [0.9-1.8]), but that could be related to an infectious process. C4 was in the reference range – 0.33 g/L [0.16-0.48].

According to the development of MOD with CNS involvement, the therapy of Eculizumab was started, and patient received it 4 times. After that her neurological state and renal function (GFR 27.2 ml/min/1.73 m^2 by Schwartz Equation) slightly improved, however, complete recovery was not made.

The laboratory data in dynamics is demonstrated in Table 1.

Patients total hospitalization period was 18 weeks. She received APD for 11 weeks, and she was fed through feeding tube for 16 weeks.

After discharging the 2 years old girl continued to receive special rehabilitation courses and antihypertensive therapy.

DISCUSSION

The 2 years old girl described in this study developed multiple organ damage with CNS involvement during the course of typical hemolytic uremic syndrome. She received monoclonal antibody eculizumab after 8 weeks from the onset of the disease, and had slight improvement in her neurological state and renal function, but complete recovery was not made.

The primary pathophysiologic mechanism in typical HUS is endothelial damage caused by Shiga toxin followed by activation of the complement cascade leading to thrombotic microangiopathy mainly in the kidney. Most often, kidney damage is not permanent and renal function recovers [5]. However, in the presented case patients renal function improved slightly from GFR 11.9 ml/min/1.73 m^2 by Schwartz Equation in the beginning of the disease, until GFR 27.2 ml/min/1.73 m^2 by Schwartz Equation before discharging, and complete recovery was not made.

Also other organs can be damaged in the case of typical HUS. CNS impairment develops approximately in 25-30% of cases [4, 5]. It may be due to local microangiopathy, or the neuroinflammation through massive cytokine release may play a critical role in CNS damage [7]. In the presented case patient developed neurological impairment, which involved left side hemiparesis with muscle dystonia on the right side extremities. The girl experienced atypical seizures twice, and brain MRI revealed ischemic damages in the basal ganglia and brainstem.

Although, monoclonal antibody Eculizumab is now recognized as the treatment of choice for atypical HUS [8], it is also successfully used in the cases of typical HUS with multiple organ damage and CNS impairment. The positive response with Eculizumab could be explained by the fact that in typical HUS the complement is directly activated [5, 6]. However, there are reported results, which do not support the use of Eculizumab for patients with typical HUS [9].

In the presented case, Eculizumab was used. Patient received the first dosage of monoclonal antibodies after 8 weeks from the onset of the disease. The retrospective analysis revealed that early use of Eculizumab was associated with better neurological outcome. And in patients with rapidly progressing HUS, prophylactic therapy before development of neurological symptoms may be considered [5].

The treatment of Eculizumab in our case was started when the neurological symptoms had already developed. However, patient had slight improvement in her neurological state after Eculizumab, the consequences were long-term disability.

This case confirms that the lack of common perspective on typical HUS cases with neurologic involvement may delay the start of adequate therapy and result in severe neurological sequelae. We suggest that a prospective randomized trial is needed to compare neurological

outcome with Eculizumab versus placebo treatment in children with typical HUS. And that also could help make a consensus in the pediatric typical HUS cases, which present with CNS damage.

CONCLUSION

This case shows that Eculizumab can be used when the typical HUS presents with MOD that also involved CNS impairment. However, in this case therapy with Eculizumab was started only after 8 weeks from the onset of the disease, and that may explain why the two years old girls complete recovery was not made. It can be considered that in pediatric HUS cases with neurologic involvement early Eculizumab therapy could be advantageous in reducing long-term neurological sequelae.

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ABBREVIATIONS

APD – automated peritoneal dialysis
EHEC – enterohemorrhagic E.coli
HUS – hemolytic uremic syndrome
MOD – multiple organ damage
MRI – magnetic nervous system
STEC – Shiga toxin-producing E.coli
tHUS – typical hemolytic uremic syndrome

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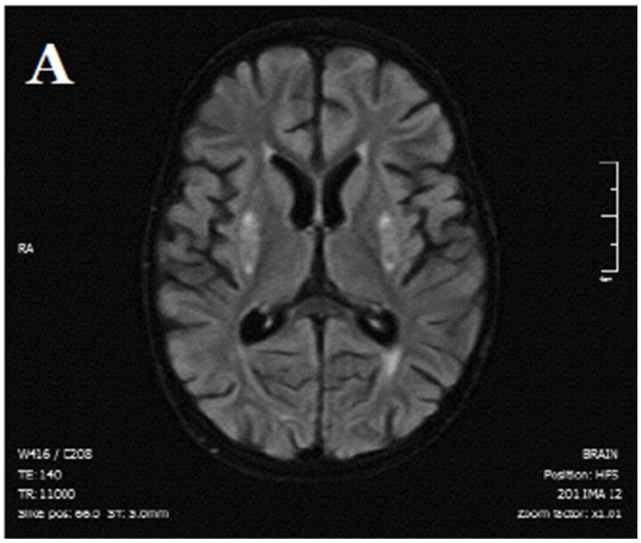
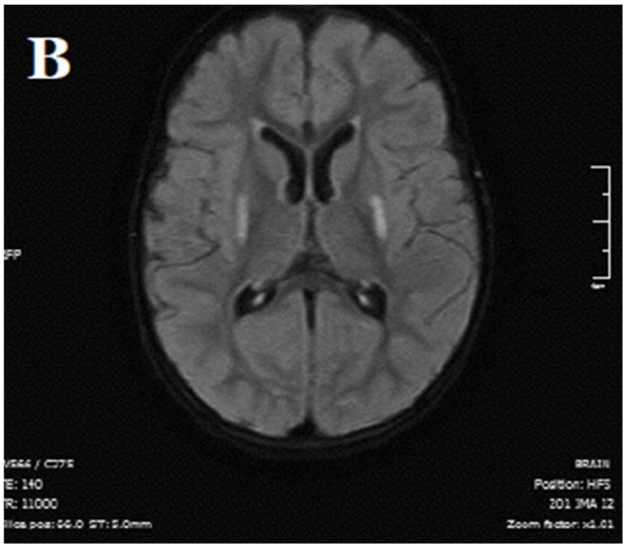
TAB. 1. LABORATORY DATA IN THE DYNAMICS.

	Hospitalization day	Before discharging
WBC (10^3/uL)	21.66	8.09
RBC (10^6/uL)	3.01	3.55
HGB (g/dL)	8.3	10.1
PLT (10^3/uL)	48	260
CRP (mg/L)	49.16	0.77
SCr (mcmol/l)	365.46	163.00
Urea (mmol/l)	23.49	12.7
GFR (ml/min/1.73 m^2 by Schwartz Equation)	11.2	27.2

FIG. 1. BRAIN MAGNETIC RESONANCE IMAGING (MRI). PICTURE A: FUSED HYPERINTENSE FOCI IN THE BASAL GANGLIA (4 WEEKS AFTER HOSPITALIZATION). PICTURE B: SCARRING IN THE BASAL GANGLIA (17 WEEKS AFTER HOSPITALIZATION).

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