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Case Report

Ophthalmoplegia in the Acute Phase of Hemolytic Uremic Syndrome: A Case Report

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ABSTRACT

Hemolytic uremic syndrome (HUS) is a common form of thrombotic microangiopathies. Among its extrarenal complications, ocular involvement is very rare.
We present a patient with HUS, whose first symptom was isolated abduction deficits in the eyes. Lethargy was added during the clinical course, suggesting neurological involvement. Although conventional magnetic resonance imaging was normal, symmetric diffusion restriction was detected in bilateral putamen on diffusion-weighted images. Treatment with peritoneal dialysis, fresh frozen plasma infusions, and eculizumab was initiated. The patient responded well to the treatment and was discharged with excellent neurological, hematological, and ophthalmological outcomes. Nephrological follow-up is being continued due to proteinuria
To our knowledge, presenting with ophthalmoplegia in the acute phase of hemolytic uremic syndrome is very rare. The patient's ophthalmological and neurological symptoms improved after eculizumab treatment. We suggest that eculizumab is effective in the acute phase of HUS in cases of ophthalmological involvement.

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a common form of thrombotic microangiopathy. It is characterized by hemolytic microangiopathic anemia, thrombocytopenia, and acute renal failure.[1,2] New researches on genetic mutations on the alternative pathway of the complement ensured a better understanding of the underlying causes.[3,4] As a result of these researches, the classification changed. The new classification is based on pathophysiological considerations and triggering factors.[3] The initial management of HUS is supportive, based on appropriate electrolyte and fluid management, erythrocyte, and platelet transfusions when indicated. Dialysis should be initiated in the presence of symptomatic uremia, azotemia, severe fluid overload, or electrolyte abnormality that is refractory to medical therapy. Plasmapheresis and eculizumab are other treatment options in atypical forms. Since the complement-regulated abnormalities play a key role in the mechanism of atypical-HUS, eculizumab is used as a highly effective therapy, which is a monoclonal C5-inhibitor antibody.[4]

The most common extrarenal complication is neurological involvement, and magnetic resonance imaging (MRI) is the most sensitive diagnostic technique especially in the diagnosis of non-hemorrhagic central nervous system (CNS) lesions. Main conventional-MRI findings in children are symmetric lesions of

basal ganglia (BG) or extensive cortical and/or subcortical lesions, which may be reversible or not.[5] Although features of conventional-MRI findings are well known, abnormalities of diffusion-weighted images (DWI) have been reported in only a few cases. Of the extrarenal complications, ocular involvement is infrequent. Previous ocular findings are retinal, choroidal, and vitreal hemorrhages and ischemic signs like cotton wool spots, retinal whitening, and non-perfusion zones.[6] In the literature, a case presented with isolated ophthalmoplegia in the acute phase and diffusion restriction in the BG without conventional-MRI abnormality has not been reported yet.

Herein we reported a four-year-old boy with atypical-HUS who responded well to eculizumab. The patient's first symptom was isolated ophthalmoplegia, and DWI revealed bilateral symmetric diffusion restriction in putamen without conventional-MRI abnormality.

CASE REPORT

The informed consent was taken from the parents. Four days before the presentation to our clinic, a four-year-old boy had been hospitalizing due to abdominal pain and vomiting in another hospital. He was referred with acute ophthalmoplegia. Physical examination revealed hypertension (130/90 mmHg), bilateral periorbital edema, and abduction deficits in the eyes (Figure 1a). Fundus examination revealed no abnormality. Laboratory investigations showed elevated blood urea nitrogen (BUN), creatinine and uric acid, proteinuria, hemolytic anemia, and thrombocytopenia (Table 1). Peripheral blood smear revealed schistocytes, fragmented erythrocytes, and thrombocytopenia. Hemolytic anemia, thrombocytopenia, acute renal injury indicated HUS. In 24-hour urine collection, nephrotic-range proteinuria (279 mg/m²/h) was detected. ADAMTS-13 activity was revealed higher than 10%, and the stool testings for *Escherichia coli (E.coli)* O157: H7 and polymerase chain reaction (PCR) for Shiga Toxin-producing E. Coli (STEC) were negative. Fresh frozen plasma (FFP), sulbactam-ampicillin, and allopurinol treatments were started. Short-acting and long-acting calcium-channel-blockers were administered due to severe hypertension. On the second day, lethargy was developed, and brain-MRI was performed. DWI revealed bilateral symmetric diffusion restriction in putamen compatible with cytotoxic edema (Figure 2a-b), while conventional-MRI and MRI-angiography showed no ab-

Figure 1. (a) Abduction defisits in the eyes, (b) Improvement of abduction deficit in the eyes after eculizumab treatment (Informed consent was taken from the guardian)

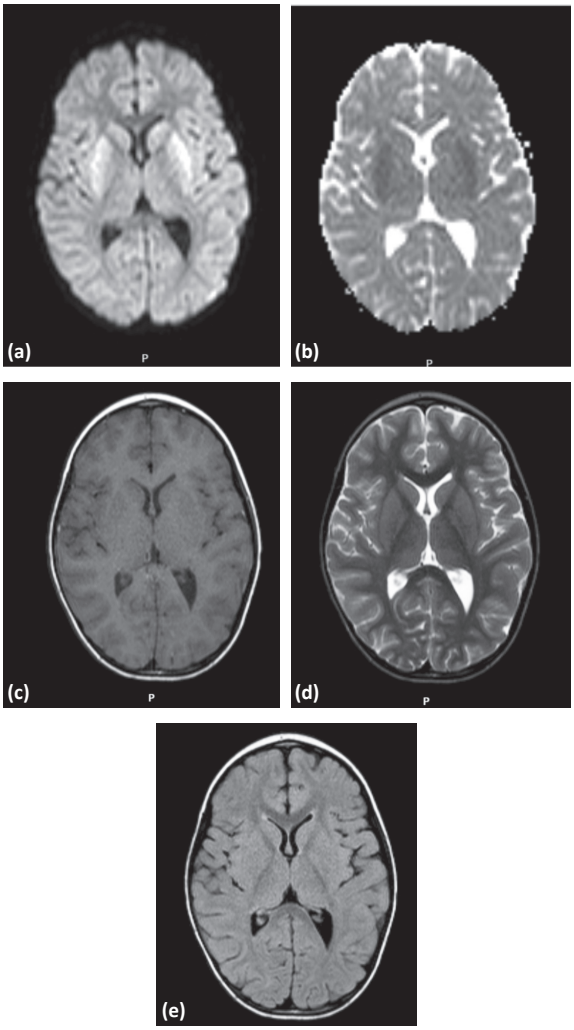

Figure 2. (a) Restricted diffusion of bilateral putamen as high signal on DW isotropic image and (b) low signal on ADC map (c) Normal conventional MRI findings, T_1 weighted axial images, (d) Normal T_2 weighted axial images, (e) Normal FLAIR-weighted images

Table 1. Laboratory results

	Laboratory results at the time of admission to the hospital	Laboratory results at the time of discharge
Hemoglobin	8,7 g/dL	9.4 g/dL
White blood cell	11.39x10³/uL	8.09x10³/uL
Platelets Count	48000/mm³	417000/mm³
Blood Urea nitrogen	62.15 mg/dL	35.51 mg/dL
Creatinine	3.28 mg/dL	0.65 mg/dL
Total bilirubin	2.77 mg/dL	0.57 mg/dL
Indirect bilirubin	2.11 mg/dL	0.43 mg/dL
Lactate dehydrogenase	2640 U/L	227 U/L
Uric acid	9.2 mg/dL	5 mg/dL
Alanine aminotransferase	154 U/L	15 U/L
Aspartate aminotransferase	67 U/L	30 U/L
C3	1.29 mg/dL	
Urine protein	+++	++
Urine hemoglobin	+	-

normality (Figure 2c-d-e). Given the negative results of stool PCR and culture, atypical-HUS was thought. Due to the neurological involvement of atypical-HUS, after vaccination of meningococcus, eculizumab was administered according to pediatric dose recommendations. Peritoneal dialysis (PD) was initiated on the day of 5, owing to anuria and progressive azotemia. The patient's ophthalmoplegia (Figure-1b) and neurological symptoms improved on the day of four, after eculizumab. After eculizumab, six times of erythrocyte transfusion, 15 days of FFP infusions, ten days of allopurinol, and 12 days of PD, the patient was discharged with normal hematological, ophthalmological, and neurological findings (Table 1). Nevertheless, since persistent proteinuria, nephrological follow-up is being continued.

DISCUSSION

The extrarenal complications of HUS involve the gastrointestinal system, extremities, heart, lung, eyes, and CNS. Neurological involvement is the most frequent extrarenal complication and occurs in about 20-50% of HUS patients. The pathophysiology of neurological involvement is unclear, though a toxin-mediated vasculopathy in small vessels is considered to be the postulated mechanism.[7] The most common signs of neurological involvement are seizures, visual disturbances, alterations of consciousness, hemiparesis, and brain-stem symptoms. The prognosis is variable, and predicting the neurologic outcomes is difficult in the acute phase. Clinical outcomes may be favorable even in patients with severe MRI findings, except for hemorrhagic lesions. Although computed tomography is a sensitive tool, especially for hemorrhagic lesions, it may be normal in the acute phase in cases of non-hemorrhagic lesions. MRI is more sensitive to the neurological involvement of HUS. Non-hemorrhagic conventional-MRI findings are symmetric BG involvement compatible with reversible edema, cortical/subcortical patchy lesions, and T2-hyperintensity lesions in white matter, especially in parieto-occipital areas, known as posterior reversible encephalopathy syndrome.[7,8] Previous studies on DWI suggested that DWI might ensure the early detection of imaging abnormalities in the neurological involvement of HUS. However, the presence of early diffusion abnormality findings was not valuable in predicting neurological outcomes.[9,10] The patient had symmetric diffusion restriction in bilateral putamen on DWI with normal conventional-MRI findings in the acute phase. To our knowledge, this was the first HUS patient who had normal conventional-MRI findings with symmetric diffusion restriction in BG. This finding may support the view of DWI might ensure the detection of the earliest non-hemorrhagic CNS lesions. It is known that early use of eculizumab improves neurological outcomes.[11] Maybe the administration of eculizumab therapy contributed to the favorable neurological outcomes.

Ocular involvement is a rare extrarenal complication, and it is reported in 4% of all pediatric HUS cases. Cases reported to date regarding ocular involvement consist of vitreous hemorrhage, retinal hemorrhage, retinal artery/vein occlusion, ischemic retinopathy, neovascularization, choroidal hemorrhage, and/or optic atrophy, premacular hemorrhage, and purt-

scher retinopathy. Only one case was reported with ophthalmoplegia who had also had optic disc edema and was seen after improvement of acute atypical-HUS. The probable mechanism was asserted as thrombotic microangiopathy, which affected the optic nerve head as papillitis, and inferior rectus muscle as ophthalmoplegia, and the patient's eye findings benefitted from intravenous dexamethasone.[12] Sturm et al.[13] reported their three cases with ocular involvement (purtscher retinopathy and intraretinal hemorrhages) of HUS that two of them developed vision loss during the follow-up. As we browsed through the treatments, all of them had PD, two of them had occlusion therapy for amblyopia, and one of them had multiple sessions of pan-retinal laser photocoagulation, which was not successful. One of them who had intraretinal hemorrhages, and was treated with the only dialysis was observed complete recovery in the visual functions. David et al.[14] presented a 23-year-old woman who had bilateral severe retinal detachment during the clinical course of HUS. Since treatments with plasmapheresis, hemodialysis, and systemic steroids provided partial systemic and ocular recovery, systemic weekly eculizumab was added, resulting in complete recovery. Interestingly, our patient's first symptom was ophthalmoplegia with normal fundoscopic examination findings and he responded well to eculizumab.

To our knowledge, presenting with isolated ophthalmoplegia in the acute phase of atypical-HUS is very rare. Neurological and ophthalmological findings were ameliorated after eculizumab therapy. The probable mechanisms of ophthalmoplegia are thrombotic microangiopathic involvement of external rectus muscles, abducens nerves, or brain-stem. We suggest that isolated ophthalmoplegia may be seen in the acute phase of HUS, and eculizumab may ensure favorable outcomes in both ocular and CNS involvement.

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