International Journal of Healthcare and Medical Sciences
ISSN(e): 2414-2999, ISSN(p): 2415-5233
Vol. 4, Issue. 4, pp: 49-53, 2018
URL: http://arpgweb.com/?ic=journal&journal=13&info=aims

Academic Research Publishing Group

Original Research Open Access

Fatal Bilateral Strokes in a Child With Hemolytic Uremic Syndrome- A Potential Therapeutic Role of Eculizumab

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Abstract

Background: HUS is a life-threatening multisystem disease caused by uncontrolled complement activation. About 25 % of patients have CNS (Central nervous system) involvement, often leading to serious long-term disabilities in young children. Eculizumab, a humanized monoclonal antibody that targets the complement protein C5, has shown to improve the disease course in children with better neurological outcomes. Early use in disease course showed much better results and its potential use as a prophylactic therapy has been indicated. Scoring systems have been developed for prediction of CNS complications, which may help identify potential candidates for prophylactic Eculizumab therapy. Presentation: We present a 3 year old child who presented with Shiga-Toxin Producing E coli Hemolytic-Uremic Syndrome (STEC-HUS) and seizures. One week into hospitalization he suddenly became unresponsive besides withdrawal to pain. Brain MRI revealed multifocal infarcts involving bilateral basal ganglia, thalami, dorsal brainstem, and cerebellar white matter with microhemorrhages. He was started on Eculizumab in an attempt to halt neurological decline. In spite of starting Eculizumab therapy, our patient succumbed to a fatal cardiac arrest. Based on the SCWP (sodium, CSR, white count and protein) scoring system our patient was at very high risk for developing neurological sequelae even at initial presentation. His therapy was not started until very late in the course of the disease which may have led to the unfavorable outcome Conclusion: Ecluzimab therapy should be initiated early in HUS patients with CNS involvement. Scoring systems may help identify at risk patients and potentially start prophylactic Eculizumab therapy to achieve improved neurological outcomes in children.

Keywords: Thalamic stroke; Eculizumab; HUS; Microangiopathy; E.coli 0157:H7.

1. Introduction

Hemolytic uremic syndrome (HUS) is a multisystem disease mostly affecting children less than 5 years [1]. HUS primarily manifests as a clinical triad of renal failure, thrombocytopenia and hemolytic anemia [2]. It is caused by *Escherichia coli* serotype O157:H7 in majority of cases [3]. Shiga toxin, produced by this bacteria, leads to endothelial damage followed by activation of complement cascade which causes thrombotic microangiopathy mostly in the kidney [3]. Neurological involvement is the most common extra-renal manifestation with almost 50% of the patients with HUS [2]. It may manifest as altered mental status, seizures, cortical blindness, hemiparesis or other focal neurological deficit. Neurological symptoms may be multifactorial secondary to hyponatremia, hypertension or cerebral microangiopathy [1]. CNS (central nervous system) involvement is associated with high morbidity and mortality [2]. Brain magnetic resonance imaging (MRI) typically show acute involvement of basal ganglia and thalamus or the supratentorial white matter [1]. Early initiation of eculizumab therapy in patients with HUS and CNS involvement, has shown to improve neurological outcomes [2, 3]. We present a 3 year old patient who had a severe presentation of typical HUS with bilateral thalamic infarcts. He received one dose of eculizumab, later in the course of disease, but succumbed to a fatal cardiac arrest.

2. Case Presentation

A three year old unimmunized boy presented to his local ED with two day history of fever and bloody diarrhea. On initial evaluation he appeared lethargic and was hypoxemic, so got transferred to our pediatric ICU for further management. On admission his sodium was 126, BUN 65, creatinine 2.6, protein 5.3, albumin 1.9, WBC 31, platelets 74, CRP 19. As he lived on a cattle ranch and family did consumed unprocessed food his stool was tested for E.Coli. His stool tested positive for Shiga toxin producing E.coli (STEC). ADAMTS 13 activity (ADAM metallopeptidase with thrombospondin type 1 motif 13) was normal, C3 and C4 levels were normal. He was diagnosed with Diarrhea + Hemolytic uremic syndrome (HUS) and started on hemodialysis with transition to continuous renal replacement therapy (CRRT). Within the next 24 hours he had a generalized tonic clonic seizure. CT head was normal, EEG just showed diffuse slowing with no epileptiform discharges but sodium had dropped further to 123. He was started on 3% saline with gradual increase in serum sodium. He was also started on levetiracetam following 2 more brief seizures. He continued to remain febrile and his WBC rose from 31 on

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admission to 66. He was started on prophylactic antibiotics for possible sepsis. Over the next few days he had no more seizures but was agitated. On 7th day of admission he had acute change in mental status where he became unresponsive to painful stimuli, tachypneic and tachycardic. Brainstem reflexes were intact and no focal deficits were noted. A STAT brain MRI showed multifocal infarcts involving bilateral basal ganglia, thalami, dorsal brainstem, and cerebellar white matter with microhemorrhage (Figure 1,2). With these findings he was started on Eculizumab therapy to try to slow down disease progression and improve neurological status. His respiratory and cardiac status continued to decline over the next 48 hours. His echocardiogram did not show any significant cardiac dysfunction. On day 9 he had a cardiac arrest and could not be resuscitated.

3. Discussion

Hemolytic uremic syndrome (HUS) is defined by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Shiga toxin-producing Escherichia coli O -157 is a major cause of HUS and most commonly affects young children less than 5 years old [1]. Neurological complications affect 20 –50% of patients and often imply a poor prognosis with increased mortality and morbidity [4]. Shiga toxin starts a pathogenic cascade leading to thrombotic microangiopathy (TMA) in the kidney. The pathophysiology of neurological involvement in HUS is thought to be multi-factorial. Cerebral TMA which was thought to play a key role, was found only in a minority of HUS patients on autopsy [5]. A multi-faceted pathology was also supported by animal studies, where cerebral TMA was absent in animals with HUS and neurological complications [6]. Shiga toxin acting directly on the endothelial and neuronal cells, in combination with electrolyte imbalance, uremia and hypertension, have been proposed as integral mechanisms for neurological involvement during HUS. [2].

CNS involvement mostly manifests as stupor/coma, seizures, hemiparesis, visual disturbances or other focal neurological deficits [2]. Our patient initially had some decreased alertness, this could have been the first sign of neurological involvement, however was attributed to dehydration and electrolyte abnormality. His seizure was also thought to be provoked from hyponatremia as his CT head showed no signs of abnormality and EEG was not epileptiform. EEG recordings in patients with HUS have mostly shown non-specific diffuse slowing of background, only rarely showing epileptiform abnormalities. Majority of patients have normalization of EEG by 6 months with about 20% still showing nonspecific slowing even in absence of any clinical symptoms. Status epilepticus including non-convulsive status was not detected in any patient [2]. Patients with neurological involvement may show variable MRI pattern, T2 and DWI hyperintensities in the basal ganglia, thalamus and extending into the white matter [1]. Parieto occipital white matter T2 hyperintensities, extending into the white matter and cortical watershed cerebral area is seen in reversible posterior leukoencephalopathy (PRES). T1 hyperintense lesions may represent regions of hemorrhagic conversion or coagulative necrosis secondary to microthrombi [7]. Our patient showed a similar radiological picture with bilateral thalamic and basal ganglia diffusion restriction and micro-hemorrhagic changes. He did not have evidence of PRES on initial CT or the later MRI.

Yamamoto, *et al.* [8] looked at risk factors to predict neurological involvement in patients with typical HUS. They found that high WBC and CRP at presentation in addition to lower sodium and serum protein, indicated higher risk for neurological involvement [4]. A scoring system – SCWP (sodium CRP, WBC and protein) score has also been developed to predict CNS involvement in a patient presenting with HUS. Typical HUS patients with neurological complications were noted to have higher SCWP scores as compared to those without. [4] The scoring system is not widely used in clinical practice yet and was not implemented in our patient. However, in retrospect, our patient presented with a very low sodium, high CRP, very high WBC and low protein level. If the scoring had been used it would correctly identify our patient at high risk for neurological involvement.

Treatment of HUS is mostly supportive with no proven treatment for neurological complications. Correcting electrolytes, dialysis, preventing hypertension and early correction of fluid deficit are the mainstay of therapy [9]. A large double blind randomized control study of 120 patients with HUS showed no significant benefit of corticosteroids vs placebo in preventing renal, neurological, or hematological complications [10]. One prospective study of 12 patients showed good outcomes with intravenous IgG in patients with neurological involvement. All 12 patients survived, with all but two, having complete neurological and renal recovery. [11]. Most studies have failed to demonstrate improvement in outcomes with plasmapheresis in typical HUS [12]. A small study with 5 patients did show benefits of early plasma exchange in five adults with HUS and neurological involvement. [13]. The difference in response can also be due to timing of initiation of therapy (early in the latter study) and severity of illness (sicker patients in the prior studies). The failure to demonstrate presence of autoantibodies in HUS, make plasmapheresis and immunoadsorptive therapy experimental/hypothetical. [11].

Eculizumab is a humanized monoclonal antibody that binds to the terminal compliment C5 and inhibits activation of complement cascade. Its use is well established to benefit in atypical HUS, which differs from typical diarrheal associated HUS, due to abnormalities in the complement regulating system as the underlying pathophysiology [3]. The pathophysiology of neurological involvement in HUS is multifactorial and the literature supporting its use was limited to isolated case reports [14]. Pape et. al in their recent case series [3] demonstrated the early use of Eculizumab to be associated with good neurological outcome in patients with typical HUS. Eculizumab is proposed to prevent the hyperactivation of compliment system seen in typical HUS and henceforth prevent complement mediated cerebral thrombotic microangiopathy [3, 15]. This study also proposed a potential role of prophylactic use of eculizimab in patients with rapidly progressive HUS to prevent long term neurological sequelae.

Our patient's clinical status worsened in spite of getting started on supportive therapy early in course of disease. Eculizumab use was discussed when patient had his first seizure. As there is no clear consensus for its use in typical

HUS and there was concern for sepsis in our unimmunized patient with escalating white count, Eculizumab was not given early on. With worsening of his neurological condition and MRI changes, Eculizumab and plasma exchange were discussed as potential interventions again. Plasma exchange does not have strong evidence to improve outcome in typical HUS patients and would have added risk of bleeding and cardiac decompensation. Looking at his overall picture we decided to immunize patient against encapsulated organisms and start Eculizumab therapy. Unfortunately, our patient did not have a good outcome. This may have been due to severity of disease, delay in starting immunomodulating therapy or cardiac involvement, even though Echocardiogram did not show significant cardiac changes.

In conclusion, HUS is a serious condition with potential life-threatening CNS involvement. Changes in the basal ganglia and thalamus are commonly seen on imaging. In addition to supportive measures, early use of Eculizumab can play a potential therapeutic role in preventing cerebral thrombotic microangiopathy, leading to better neurological outcomes. Use of predictive risk factors or scores may even help select patients who would benefit from prophylactic Eculizumab therapy. Randomized controlled studies in the future are needed to help establish this.

4. Abbreviations

HUS- hemolytic uremic syndrome
CNS- central nervous system
STEC- HUS- Shiga-Toxin Producing E coli Hemolytic-Uremic Syndrome
MRI- magnetic resonance imaging
ICU- intensive care unit
BUN- blood urea nitrogen
CRP- C-reactive protein
WBC- white blood cell
CRRT- continuous renal replacement therapy
TMA- thromobotic microangiopathy
CT- computerized tomography
EEG- electroencephalogram
DWI- diffusion weighted imaging
PRES- posterior reversible encephalopathy syndrome

Illustrations

Figure-1. axial DWI image showing diffusion restriction from bilateral acute basal ganglia strokes

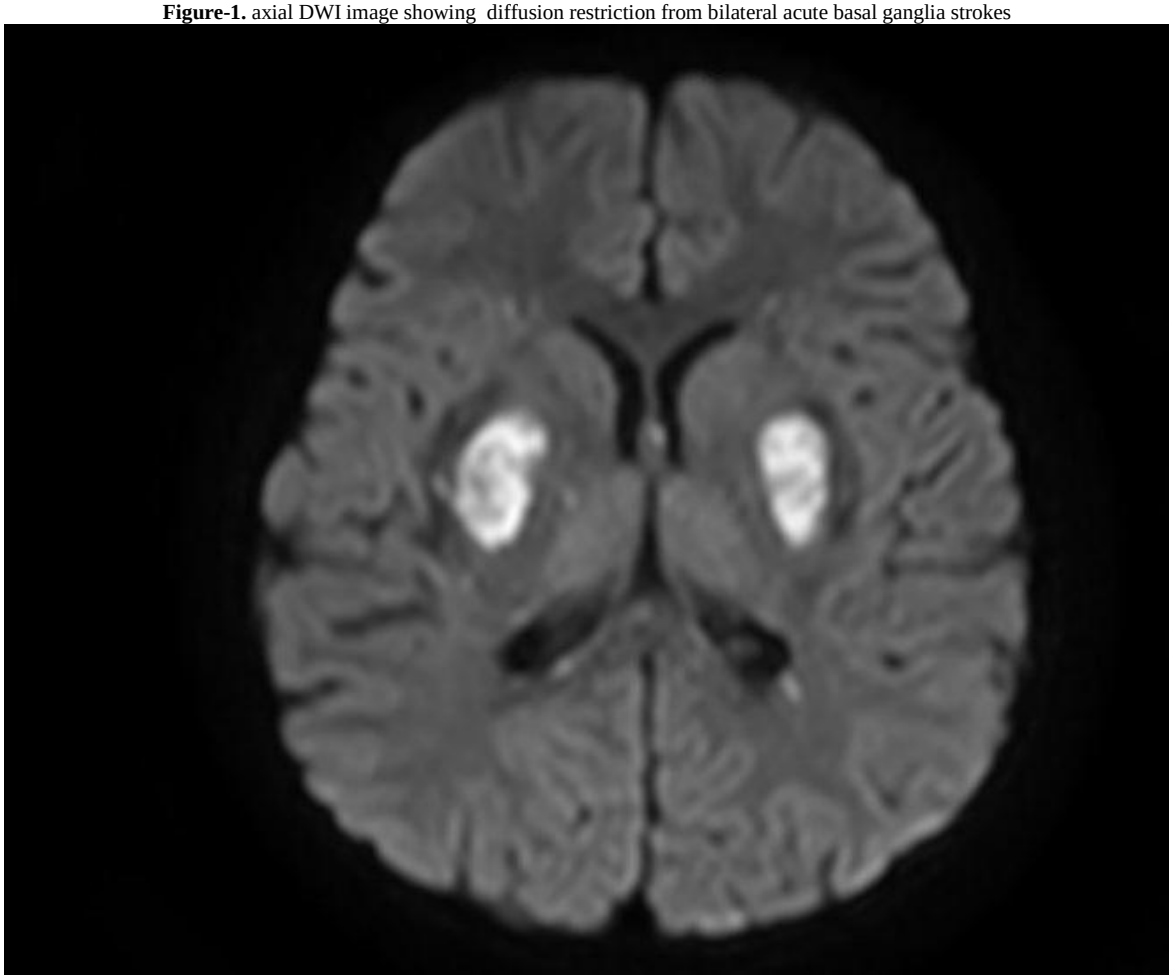
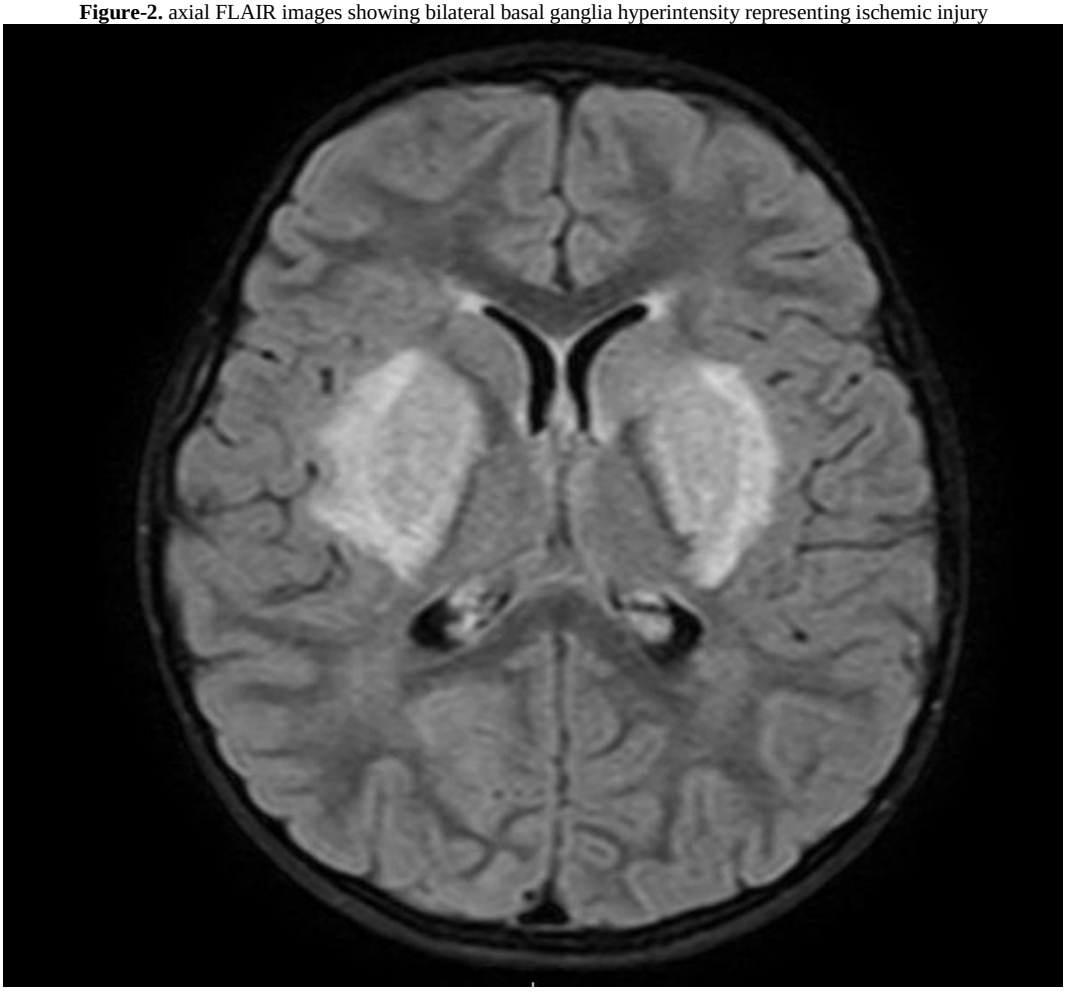


Figure-2. axial FLAIR images showing bilateral basal ganglia hyperintensity representing ischemic injury



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