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## Case Report

# Hemolytic uremic syndrome with central nervous system manifestations, a case report and literature review ☆,☆☆

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## ABSTRACT

Hemolytic uremic syndrome (HUS) is a multisystem disorder generally seen in children and young adults, manifesting with the symptomatic triad of thrombocytopenia, hemolytic anemia, and acute kidney injury. These symptoms are often preceded by a prodrome of bloody diarrhea, vomiting, fever, and weakness. HUS is an exceedingly rare entity, with less than 1.5 per 100,000 people affected annually. HUS with central nervous system (CNS) manifestations constitutes approximately 20%-50% of cases and often presents with seizures, altered level of consciousness, and brainstem symptoms. CNS involvement in HUS is a major cause of acute morbidity and mortality; therefore, timely diagnosis and treatment are crucial in the management of these cases. Neuroimaging plays a critical role in the diagnosis; however, it might be very challenging in a large number of cases because studies that report the typi-

Abbreviations: HUS, hemolytic uremic syndrome; aHUS, atypical hemolytic uremic syndrome; CNS, central nervous system; STEC, Shiga toxin-producing *E*-coli; Stx, Shiga toxin; CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; ICU, intensive care unit; MCV, mean corpuscular volume; EEG, electroencephalogram; PCPC, pediatric cerebral performance category; C5, complement component 5; TNF, tumor necrosis factor; Gb3, globotriaosylceramide.

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cal neuroradiologic features of brain injury in cases with HUS are not commonly available. Herein, we demonstrate in a case-based approach, the importance of combining clinical suspicion with different radiologic modalities to better characterize HUS cases with CNS involvement, as well as demonstrate how the early start of meticulous supportive therapy can lead to a favorable outcome even when severe brain involvement is evident on acute imaging studies. Furthermore, we provide an illustrated overview of the current theories that explain the neurologic involvement in HUS, as well as the commonly affected brain areas and how this entity can be radiologically differentiated from other potential diagnoses.

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## Introduction

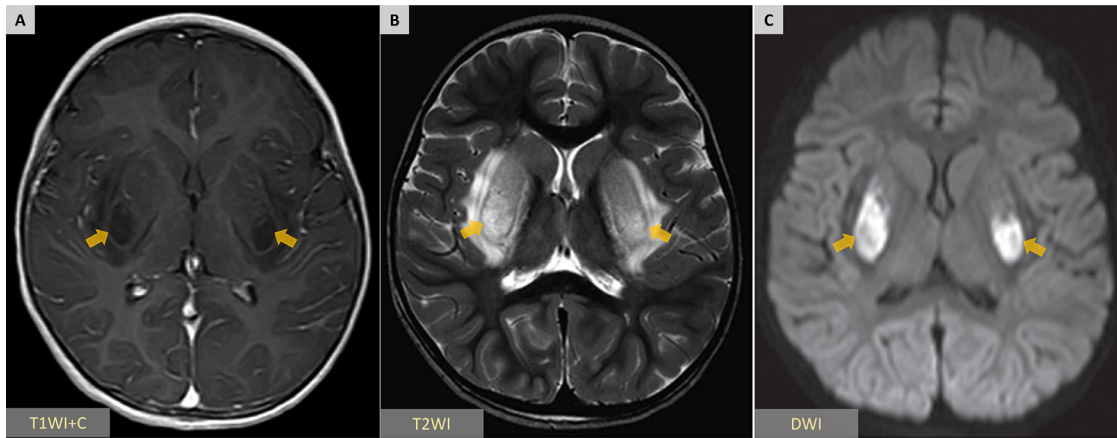
Often seen in children under the age of 10 years, with the majority occurring in those between the ages of 1 and 4 years, hemolytic uremic syndrome (HUS) is a multisystem disorder manifesting by the presence of microangiopathic thrombosis-induced thrombocytopenia, nonimmune hemolytic anemia, and acute renal dysfunction [1]. These symptoms are typically preceded by a gastroenteritis prodrome in the form of bloody diarrhea, vomiting, fever, and dehydration [2]. HUS was first defined as a syndrome in 1955 by Gasser et al. [3]. In most patients, HUS is caused by enterohemorrhagic Shiga toxin (Stx)-producing *Escherichia coli* (STEC); however, it can also be seen with *Shigella* and *Salmonella* strains, as well as pneumococcal infections [1,2]. Thus far, the most predominant serotype of STEC associated with HUS around the world is still O157:H7 [4]. The underlying mechanism is typically mediated by a Stx-induced inflammatory cascade, triggering endothelial injury and thrombotic angiopathy, mainly involving small vessels and capillaries [5]. Another existing form of the disease is called atypical HUS (aHUS), which is often due to a genetic mutation involving the complement cascade and can present differently [1,2]. However, both can result in widespread microthrombi formation in multiple organs [5,6]. The 2 principal target organs of Stx-mediated damage are the kidney and the brain. The reported rate of brain involvement in patients with HUS widely varies between 10% and 52% due to the unstrict definition of neurologic involvement among reported studies. In a recent study that involved a retrospective analysis of 202 children aged <16 years with confirmed STEC-caused HUS from 2005 to 2018, they reported a rate of 11% based on defining neurologic involvement by seizures, encephalopathy, or focal neurologic deficit, and considering features such as irritability or lethargy to be nonspecific [7]. Although brain involvement is not as common as renal involvement, it's the most common cause of mortality and a major contributor to morbidity in cases with HUS [8]. Close monitoring of central nervous system (CNS) symptoms and combining clinical suspicion with different radiologic modalities are important to identify neurologic involvement in children with HUS early in the course of their disease. Neuroradiology in children with HUS is focused mainly on the exclusion of any complicated life-threatening hemorrhage, or the identification of brain edema, and is usually done via standard CT; however, MRI can better depict HUS imaging features and disease prognosis [9], but patients are usually insufficiently stable to per-

mit a longer MRI duration. Therefore, studies that report the typical neuroradiologic features of brain injury in cases with HUS are not commonly available. In this report, we present a case of HUS with the typical neuroradiologic features of brain involvement and demonstrate that even in patients with severe brain involvement on acute imaging studies, the prognosis can be favorable for clinical outcome and resolution of pathologic imaging findings.

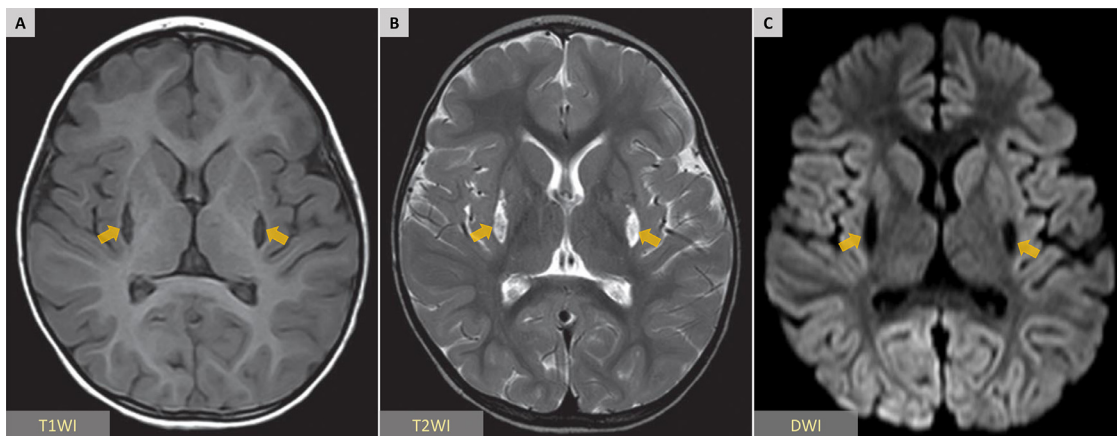
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## Case report

A 4-year-old girl presented to our emergency department with acute-onset bloody diarrhea, high-grade fever, severe dehydration, and decreased urine output. This was followed by episodes of unresponsiveness, generalized tonic-clonic seizures, and hypotonia. Metabolic studies showed elevated serum creatinine (300  $\mu$ mol), serum potassium (6.4 mmol/L), and blood urea nitrogen level (82 mmol/L). Urine analysis showed proteinuria and hematuria. Thrombocytopenia ( $41 \times 10^3$ ) and anemia (Hb = 6.2 g/dL) were evident in hematologic studies, and blood smears revealed the presence of schistocytes, which along with the reported normal MCV values suggested a hemolytic cause of the patient's anemia. Evaluation of CSF for viral encephalitis was negative. Stool sample PCR was positive for enterohemorrhagic *Escherichia coli* O157:H7 strain. CT scan of the head upon admission was unremarkable; follow-up MR imaging obtained 12 hours postadmission revealed symmetric nonenhancing, hyperintense signals demonstrating fluid restriction in the bilateral basal ganglia (Fig. 1). The patient did not have any family history suggesting metabolic or genetic conditions such as mitochondrialopathies, and screening for toxins did not reveal positive results. Therefore, based on the data obtained thus far, a diagnosis of HUS with CNS involvement was made, and the patient was admitted to the pediatric ICU, in which a meticulous supportive therapy regimen was initiated to correct the deranged metabolic profile, including plasmapheresis and continuous veno-venous hemodialysis. The patient's anemia was corrected via packed RBCs transfusion, and the platelet count was independently corrected (without transfusion) by day 10 after admission. Furthermore, the patient did not receive any antibiotic or antimotility therapies during her hospital course, but sodium nitroprusside was required for the high blood pressure. While in the ICU, an EEG was performed, which demonstrated slow background activity and diffuse



**Fig. 1(A)** – (A) Axial postcontrast T1WI of the head at the level of the basal ganglia showing nonenhancing, hypointense signal changes predominantly involving the dorsolateral lentiform nuclei (arrows). (B) Axial T2WI at the same level revealing symmetric hyperintense signals in the bilateral basal ganglia (arrows). (C) Axial DWI at the same level demonstrating diffusion restriction (arrows) along with a reduction in ADC values (not shown), consistent with cytotoxic edema. DWI: diffusion-weighted imaging.



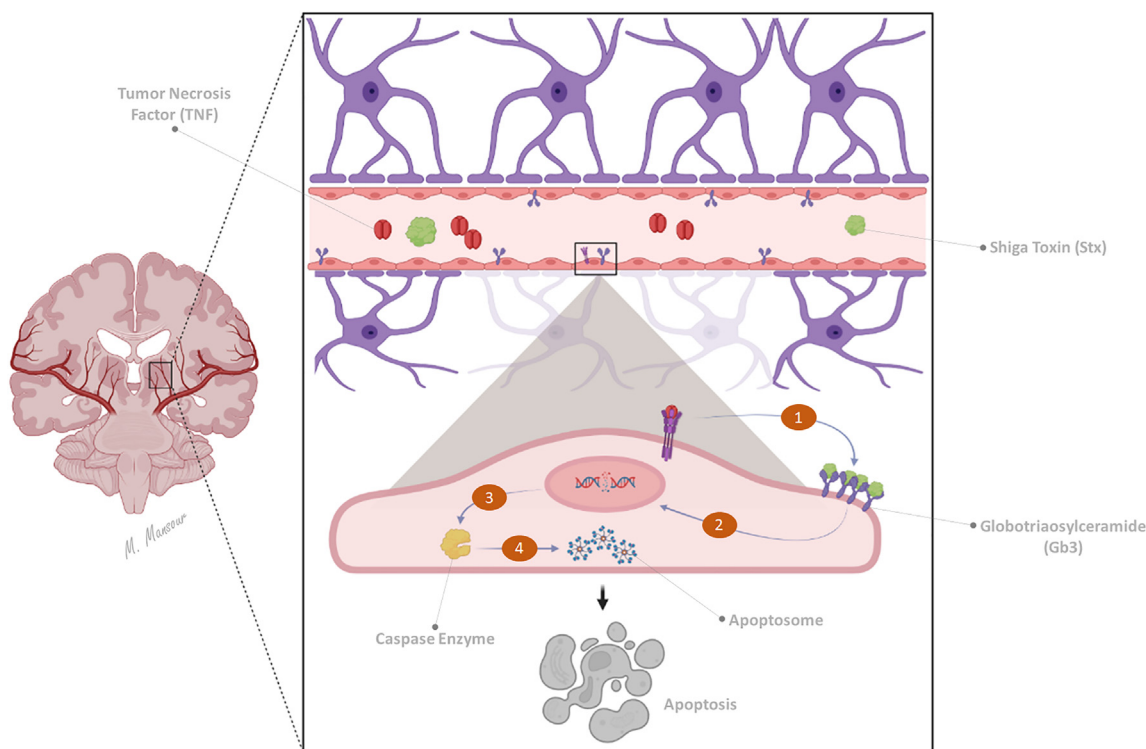
**Fig. 2(A)** – (A) Axial T1WI and (B) T2WI at the level of the basal ganglia 8 weeks after discharge revealing full resolution of the edema. Cavitations and volume loss are also noted (arrows), along with a marked resolution of diffusion restriction (C).

paroxysmal discharges. Additionally, electrical polyspikes associated with myoclonic jerks of the head were noted; therefore, the patient was started on phenobarbital, with an instant good response. The patient's neurologic status gradually improved after the correction of the deranged renal profile as evidenced by follow-up imaging performed 8 weeks after discharge (Fig. 2), which demonstrated a complete resolution of the extensive edema observed on admission; however, small cavitations evolved. The patient is currently in good general condition, with a score of "1" (ie, normal) on the pediatric cerebral performance category (PCPC) scale.

## Discussion

A clinical presentation that includes a history of acute-onset diarrhea, renal failure, and fluctuating altered level of consciousness is characteristic of HUS with CNS involvement.

Although CNS involvement is not as common as renal involvement in HUS, as discussed earlier, CNS complications are considered the main cause of mortality in these patients, a finding that is presumed to be attributed to a sudden microvascular injury involving vital areas in the brainstem, which is a commonplace of CNS involvement in HUS patients [10]. CNS involvement in HUS has been associated with a wide range of neurologic manifestations, such as lethargy, apnea, coma, seizures, cortical blindness, and hemiparesis [4,10]. Costigan et al. [7] reported that seizures were the most common presentation of CNS involvement, manifesting within 48 hours of admission to the hospital in 73% of included cases in their study, with 25% presenting with status epilepticus as the initial presentation. They additionally reported that encephalopathy was noted in 45%, while the focal neurologic deficit was evident in only 18% of the included cases [7]. Some evidence indicates a correlation between the intensity of the prodromal GIT symptoms and the severity of CNS involvement in cases with HUS; however, there are not enough data



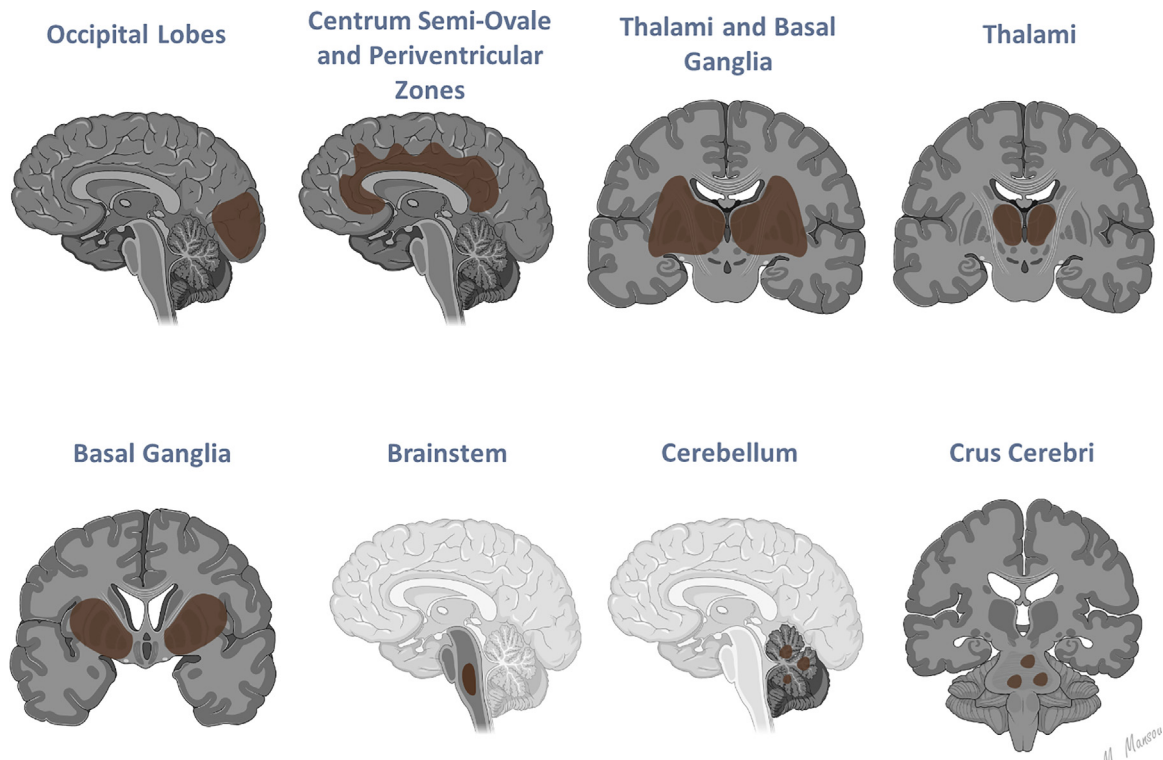
**Fig. 3 – Graphical illustration of the downstream mechanism of Stx-induced endothelial injury in brain blood vessels. TNF induces Gb3 upregulation by endothelial cells, which subsequently increases the affinity of these cells to Stx (1). Stx effect on endothelial cells involves a DNA damage response (2), which results in the activation of caspase enzymes (3) with subsequent apoptosis (4). Stx: shiga toxin, TNF: tumor necrosis factor, Gb3: globotriaosylceramide.**

to support this correlation thus far [10]. The CNS involvement in this disease is thought to be attributed to Stx-induced endothelial damage, affecting the small vessels of the brain, which results in hemorrhages and infarcts [11]. However, given the rarity of CNS involvement in HUS compared to renal involvement, other reported data suggested a combined effect of simultaneously occurring Stx-induced vascular injury, endothelial dysfunction, and nephropathy induced-hypertension and electrolyte derangements [12–15]. A critical role of tumor necrosis factor has been specifically linked and proposed as a possible underlying mechanism of the CNS involvement observed in HUS, whose higher blood concentration has been reported to be associated with brain endothelial damage. This tumor necrosis factor-mediated mechanism has been attributed to the observed relative upregulation of globotriaosylceramide (Gb3), which possesses a high affinity for Stx, leading to irreversible endothelial damage enforcing these endothelial cells to enter the apoptotic cascade as illustrated in Figure 3.

Neuroradiology plays a major role in the evaluation of HUS with suspected neurologic involvement. Computed tomography is the initial imaging modality of choice to detect associated infarcts or hemorrhages [9]. However, MRI best depicts HUS imaging features and the overall disease prognosis. On imaging, the lesions tend to have a nearly symmetric distribution pattern or less frequently, unilateral [9,11]. Most imaging studies describe the predilection for basal ganglia with involvement of the dorsolateral aspect of the lentiform nucleus

as being the most characteristic imaging finding [9], as perfectly demonstrated in our patient. Involvement of other brain areas such as occipital lobes, centrum semiovale, periventricular zones, thalami, brainstem, cerebellum, and commissural fibers has also been described in the literature as illustrated in Figure 4.

Neurologic involvement in HUS might be presented radiologically as hemorrhages, infarcts, or both. However, brain edema is typically present, which might or might not be associated with the presence of a hemorrhage or an infarct. Brain edema in HUS might be presented as cytotoxic, vasogenic, or a combination of both types. Resultant cytotoxic edema is better detected on diffusion-weighted imaging (DWI), which has been reported to correlate with the disease severity and predict areas with irreversible brain damage [9]. The increased T2 and FLAIR hyperintense signal changes in the affected white matter are often reversible and represent vasogenic edema [9]. Few case reports also describe cortical involvement with gyri-form T1 hyperintensity in the acute and subacute phases of the disease, which has been attributed to coagulative necrosis, increased protein concentration, and the presence of blood products, adding more challenge in the radiologic diagnosis of HUS in these cases due to the close radiologic similarities with other potential diagnoses, such as hypoxic-ischemic injury or necrotizing encephalopathy [9]. However, a clinical presentation of diarrhea that triggers a cascade of events in a previously healthy child with positive PCR and normal developmental milestones is specific for HUS.



**Fig. 4 – Graphical illustration of the different brain areas that have been reported to be affected in hemolytic uremic syndrome.**

Management of HUS cases with CNS involvement typically consists of prompt meticulous supportive care, generally conducted in an ICU setting to address any underlying abnormality such as hypertension and deranged renal profile, and may include renal dialysis, pulse steroids, multiple blood transfusions, and plasmapheresis [1,2]. Management must address all the detected abnormalities together because focusing mainly on a single one (even when it is the most remarkable) and ignoring others can lead to a poor prognosis. For example, Fujii et al. [16] reported a case of a young boy with posterior reversible leukoencephalopathy syndrome associated with HUS, which despite adequate blood pressure control, the syndrome did not resolve but progressed to multiple subcortical cavitations. While eculizumab, a monoclonal antibody that targets C5 protein in the complement cascade, is being used to treat cases with the atypical forms of HUS (aHUS), there is no evidence supporting its usage in the typical forms of HUS [1]. The overall mortality rate from HUS can be as low as 5%-15%, with a generally favorable neurologic outcome, especially in the pediatric age group with prompt ICU-based supportive care [1,2,11].

### Conclusions and take-home points

1. A clinical presentation that includes an acute-onset history of diarrhea, acute renal failure, and fluctuating altered

level of consciousness is characteristic of HUS with CNS manifestations.

2. Involvement of the dorsolateral lentiform nucleus, especially the putamen, is a characteristic feature of HUS with CNS manifestations and has been described in the neuro-radiology literature.
3. Treatment of HUS with CNS involvement generally depends on supportive care and may include renal dialysis, steroids, multiple blood transfusions as needed, or plasmapheresis.
4. The overall neurologic outcome of this illness is generally favorable in the pediatric age group when meticulous supportive therapy is initiated as soon as possible.

### Ethics approval and consent to participate

The approval was obtained from the Ethics Committee of Al-Azhar University Hospitals. The patient's guardians gave written informed consent to publish the case and any related data.

### Authors' contributions

M.M. was responsible for the conception of the work, data collection, drafting the article, critical revisions, illustrating figures, and obtaining approval of the final version of the

manuscript. M.H., M.R. and D.K. contributed by drafting the article, and critical revisions. M.A., A.Y. and H.A. contributed by critical revisions of the article. All authors read the final manuscript and were involved in direct patient care.

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## Patient consent

The patient's guardians gave written informed consent to publish the case and any related data.

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