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EDUCATIONAL REVIEW

Extrarenal manifestations of the hemolytic uremic syndrome associated with Shiga toxin-producing *Escherichia coli* (STEC HUS)

Myda Khalid[1] · Sharon Andreoli[1]

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Abstract
Hemolytic uremic syndrome is commonly caused by Shiga toxin-producing *Escherichia coli* (STEC). Up to 15% of individuals with STEC-associated hemorrhagic diarrhea develop hemolytic uremic syndrome (STEC HUS). Hemolytic uremic syndrome (HUS) is a disorder comprising of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. The kidney is the most commonly affected organ and approximately half of the affected patients require dialysis. Other organ systems can also be affected including the central nervous system and the gastrointestinal, cardiac, and musculoskeletal systems. Neurological complications include altered mental status, seizures, stroke, and coma. Gastrointestinal manifestations may present as hemorrhagic colitis, bowel ischemia/necrosis, and perforation. Pancreatitis and pancreatic beta cell dysfunction resulting in both acute and chronic insulin dependant diabetes mellitus can occur. Thrombotic microangiopathy (TMA) in cardiac microvasculature and troponin elevation has been reported, and musculoskeletal involvement manifesting as rhabdomyolysis has also been described. Extrarenal complications occur not only in the acute setting but may also be seen well after recovery from the acute phase of HUS. This review will focus on the extrarenal complications of STEC HUS. To date, management remains mainly supportive, and while there is no specific therapy for STEC HUS, supportive therapy has significantly reduced the mortality rate.

Keywords Shiga toxin · Hemolytic uremic syndrome · STEC HUS · Extrarenal manifestations · Seizures · Stroke · Pancreatitis · Diabetes mellitus

Introduction

Hemolytic uremic syndrome (HUS) is defined as a triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. In the USA, most cases of diarrhea-associated HUS are due to Shiga toxin-producing *Escherichia coli* (*E. coli*) 0157:H7. However, other strains of *E. coli* with different serotypes are emerging as additional pathogens that can cause HUS.

Shiga toxin-producing *E. coli* (STEC)-associated HUS (STEC HUS) is a common cause of acute kidney injury in children and can lead to significant morbidity and mortality in the acute phase. Renal involvement is present in all patients with hemolytic uremic syndrome presenting as kidney injury due to thrombotic microangiopathy (TMA) and as many as 50% of the patients require some form of renal replacement therapy. The extrarenal manifestations in affected patients can present as central nervous system (CNS), gastrointestinal (GI), pancreatic, musculoskeletal, and cardiac involvement. Table 1 summarizes the list of extra-renal complications, their manifestations, pathology findings and management. This article will focus on the extrarenal manifestations observed with *E. coli* infections causing HUS.

Pathophysiology

E. coli O157:H7 is the serotype frequently isolated from children with *E. coli* gastrointestinal infections and has a strong association with HUS in the USA [1]. In Germany, in 2011, a very large epidemic of STEC HUS was caused by an uncommon *E. coli* serotype O104:H4 for which contaminated sprouts were thought to be the vector [2]. Other strains of *E. coli* are emerging as pathogens that can trigger STEC HUS [3]. HUS has been reported in rare cases of

✉ Myda Khalid
khalidm@iu.edu

[1] Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, USA

Table 1 Extrarenal involvement in Shiga toxin-producing *Escherichia coli* (STEC HUS) by organ system

	Manifestation	Pathology findings	Management
Central nervous system involvement	• Irritability • Lethargy • Confusion • Altered mental status • Seizures • Stroke • Coma • Other rare manifestations: hemiplegia, cortical blindness, dysphasia diplopia, facial nerve palsy	– Microvascular thrombosis resulting in focal areas of infarction and necrosis – Parenchymal hemorrhage – Cerebral edema	Supportive: – Anti-seizure medications if needed – No clear data supporting the use of plasma exchange or eculizumab
Gastrointestinal complications:			
1. Intestinal	• Bowel ischemia • Bowel necrosis • Bowel wall thrombosis • Perforation • Pseudomembranous colitis • Rectal prolapse • Long term: bowel strictures/adhesions	– Bowel wall edema, necrosis and hemorrhage	– Surgical intervention such as bowel rest or bowel resection may be required
2. Hepatic	• Elevated transaminases • Elevated bilirubin in part due to hemolysis	– Thrombotic microangiopathy	– Observation only
3. Pancreatic	• IDDM in the acute and long-term setting • Pancreatic enzyme elevation • Pancreatitis • Pancreatic necrosis	– Thrombotic microangiopathy resulting in tissue necrosis	– IDDM: treat elevated blood sugars – Pancreatitis: bowel rest
Cardiovascular complications	• Hypertension • Pericardial effusion and tamponade • Depressed myocardial function	– Hypertension: volume overload, electrolyte imbalance – TMA resulting in tissue ischemia and necrosis – Myocarditis and pericardial effusions	– Hypertension: antihypertensive agents – Depressed myocardial function: circulatory support (please see Table 3 for details)
Rare case reports			
Ocular involvement [34, 35]	• Retinal hemorrhages and ischemic lesions		
Rhabdomyolysis [36, 66]	• Progressive muscle tenderness and weakness in the setting of HUS	– Muscle biopsy showed segmental rhabdomyolysis with fibrin thrombi (Fig. 11)	

IDDM insulin-dependent diabetes mellitus, *TMA* thrombotic microangiopathy

Streptococcus pneumoniae, *Shigella dysenteriae*, and *Citrobacter freundii*-associated infections. HUS can also occur without an infectious trigger in the presence of abnormalities in the complement pathway and in this setting, is called atypical HUS.

HUS develops in approximately 15% of individuals who have diarrhea secondary to STEC [1]. STEC HUS is characterized by TMA that results in microthrombi formation in the small vessels of several organs, particularly the renal microvasculature. Acute kidney injury and complications involving other organ systems in STEC HUS are primarily due to TMA. In the presence of TMA, thickening of arterioles and capillaries along with swelling and detachment of the vascular endothelial cells is observed [4]. *E. coli* possessing the plasmid that produces Shiga toxin (Stx) can produce Stx-1 and/or Stx-2. Most children who develop HUS have been infected with *E. coli* that produce Stx-1 and Stx-2 or Stx-2 alone; *E. coli* that produce Stx-1 alone are not usually associated with STEC HUS.

The precise mechanism of transport of Stx from the colonic cells to the target organs is not completely understood. It is speculated that *E. coli* adhere to intestinal mucosal cells during an infection and release Stx that causes damage to the colonic blood vessels thereby providing a passage for Stx to enter the bloodstream and reach target organs [4]. The Stx binds to cells expressing glycosphingolipid globotriaosylamide (Gb3Cer) receptors [4]. Gb3Cer receptors are expressed in kidney tissue and their binding to Stx results in the pronounced involvement of renal

microvasculature [5]. Variable expression of cellular Gb3Cer receptors in different organs may be the reason for organ-specific responses to Stx [6]. After binding to the Gb3Cer receptor, the Stx is endocytosed and causes intracellular inhibition of protein synthesis, which in turn results in apoptotic cell death [4]. Increased intracellular cytokine levels also contribute to this process [4]. The endothelial cell death triggers a cascade of events resulting in microvascular dysfunction with leucocyte attraction, fibrin deposition, and microthrombus formation. Leucocytes and neutrophils interact with the damaged endothelial cells which in turn compound the inflammation and exacerbate microvascular injury [7].

Central nervous system involvement

Epidemiology

The incidence of neurological disease with STEC HUS has been reported to be approximately 17–34% [8–10]. Neurological involvement is of particular importance because it has been associated with greater disease severity and a higher mortality [11, 12]. Irritability and other CNS abnormalities are considered the fourth manifestation of HUS. Patients with neurological involvement can present with a vast array of neurological complications that are discussed in more detail in the "Clinical manifestations" section.

Pathophysiology

The precise mechanism for neurological findings remains unclear. It is most likely a combination of Stx-induced vascular injury and endothelial dysfunction along with cytokine release in the setting of metabolic derangements and/or hypertension. Recently, interesting experiments show that neuronal cell death is much more severe in the presence of an inflammatory response [13]. Human brain microvascular endothelial cells that are pretreated with tumor necrosis factor alpha, interleukin 1-beta, n-butyric acid, and cAMP analogs have a higher susceptibility to Stx [13].

Autopsy findings are consistent with hypoxic ischemic lesions and associated cerebral edema in the majority of children studied, and there is also evidence of thrombotic microangiopathy in most but not all cases [10, 14, 15]. As expected, in some cases, large areas of hemorrhagic stroke and infarctions have been observed [15].

Clinical manifestations

In a retrospective multicenter study by Nathanson et al., 9 of 52 (17%) patients with neurologic involvement died, 12 patients had severe disabilities (23%), 5 had mild sequelae, and 26 (50%) patients had a complete recovery [11]. The most frequent neurological abnormalities in the 52 patients were altered mental status in 44 patients, seizures in 37 patients, and pyramidal and extrapyramidal symptoms in 27 and 22 patients, respectively [11]. Twelve patients had coma in addition to other neurological symptoms [11]. Some patients also demonstrated limited neurological abnormalities such as diplopia, dysphasia, and facial palsy [11]. In their study, the authors also observed that any region of the central nervous system could be involved [11]. Diffuse damage to several brain structures present simultaneously correlated with severe disabilities in most but not all patients [11]. Apart from this observation, there were no specific changes or abnormalities noted on MRI imaging early in the course of HUS with neurological involvement that would be predictive of poor neurological outcomes later in the course.

Treatment

At the current time, there is no specific treatment for neurological involvement. Treatment with anti-seizure medications is almost universal; however, it does not modify the underlying pathophysiology. Plasma exchange is not considered to be beneficial in the setting of STEC HUS, where the neurological damage is due to microvascular thrombosis and possibly direct toxicity of Stx. Plasma exchange was performed during the 2011 outbreak of *E. coli* O104:H4 in Germany in one center on a subset of patients and was not associated with improved outcomes [16]. In fact, in the study, it was observed that plasma exchange was associated with worsening neurological symptoms and deterioration in renal function [16]. Similarly, in a large prospective study of 619 children with HUS, a subset of 38 children received plasma exchange and a significant association was found between plasma exchange and the presence of hypertension, neurological symptoms, and a need for dialysis [17]. However, it is important to note that patients receiving plasma exchange in both studies were most likely patients with more severe disease, making it difficult to determine if worsening neurological symptoms and renal involvement were a result of severe HUS versus the use of plasma exchange. In a small five patient study in adults with STEC HUS, plasma exchange was found to be beneficial; however, because this finding has not been replicated in larger studies, and because additional studies show no benefit of plasma exchange, caution should be used in interpreting plasma exchange as a beneficial therapy based on the results of this study alone [18].

There is experimental evidence for the potential role of complement abnormalities in STEC HUS [19]. Eculizumab is a monoclonal C5 antibody that blocks the terminal complex in the complement cascade and is being used with excellent outcomes in individuals with complement-mediated atypical HUS. The benefit of eculizumab in STEC HUS, however,

remains unclear at this time. A favorable outcome was initially described in case reports describing the use of eculizumab in children with severe cases of HUS during a 2011 outbreak of STEC HUS in Germany; however, in these reports, a control group was lacking [20]. Subsequent studies indicate that eculizumab does not result in better outcomes [21, 22]. In order to determine if there is benefit from eculizumab in STEC HUS, additional studies are needed.

Long-term outcomes

While some patients recover completely from the neurological insult, others may be left with long-term damage. Signorini et al. report the case of a 20-month-old girl who developed diarrhea-positive HUS and had severe neurological impairment including seizures, coma, fixed midriasis, blindness, aphasia, strabismus, and motor deficits [23]. Figure 1 shows the MRI findings a week after presentation showing widespread brain involvement. Surprisingly, the patient's neurological symptoms had completely resolved by day 35 of hospitalization and she had no residual neurological deficit at 18 months of follow-up [23]. Figure 2 is her MRI at 10-month follow-up that shows almost all the CNS involvement noted on initial MRI had resolved.

Patients suffering from stroke and severe neurological damage during the acute illness are likely to have long-term neurological damage. The outcomes in children without strokes or severe anatomical damage to the brain are not entirely clear with studies demonstrating conflicting results. In a study by Schlieper et al., 22 children with neurological involvement with HUS were tested 2 years later and noted to have lower cognitive and achievement scores compared to matched controls [24]. However, a study evaluating similar outcomes in seven children found no significant cognitive deficit at the 7-year mark [25]. Long-term neurological outcomes in children with STEC HUS who did not have any neurological involvement at the time of discharge were assessed in another study performed by Schlieper et al. [26]. The children were tested on average 4 years after the acute episode of HUS, and reassuringly, no evidence for an increased risk of learning disability, behavior, or attention was found [26].

Bauer et al. evaluated long-term neurological sequelae in children with *E. coli* O104:H4-associated HUS by tracking electroencephalogram (EEG) abnormalities and reported changes in overall performance, as well as cognition/behavior and physical strength [27]. These variables were assessed at the 3- and 6-month mark after acute HUS. All three variables showed an improvement over time [27]. At the 3-month follow-up, EEG abnormalities such a mild to moderate slowing of background activity were observed in 35% of the patients, reduced performance was reported by 67%, behavioral/cognitive changes reported by 55%, and physical symptoms such as lack of strength and fitness were reported by 50% of the patients [27]. Individuals with CNS

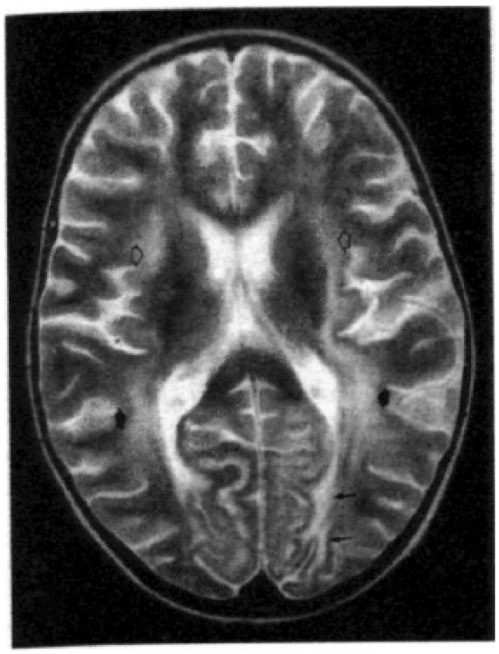

Fig. 1 MR image obtained 1 week after admission in a child with STEC HUS who had coma and seizures. T2-weighted axial image shows high signal intensity in subcortical white matter of the occipital lobe (thin black arrows), in peritrigonal white matter (thick black arrows), and external capsule (open arrows) bilaterally. Reprinted with permission from Signorini et al. [23]

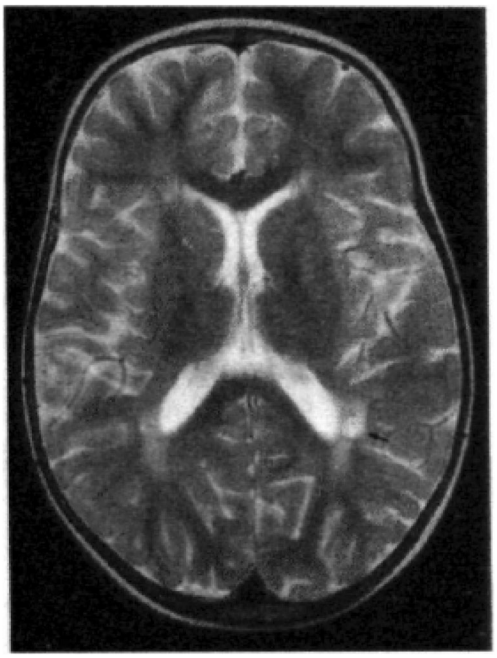

Fig. 2 MR-weighted image obtained 10 months after the onset of the symptoms, T2-weighted axial image shows a small area of high intensity signal in the left peritrigonal white matter (arrow). Reprinted with permission from Signorini et al. [23]

involvement during the acute illness had a slightly higher incidence of the previously described complaints and EEG abnormalities [27]. At the 6-month follow-up, all of the symptoms had improved with EEG changes in 19% of the patients, reduced performance reported by 44%, cognitive/behavioral changes were reported by 36%, and a lack of physical strength described by only 10% of the patients [27]. At 6–9-month follow-up, neuropsychological testing was performed and showed slightly lower global intelligence quotient (113.4 + 2.8 vs 119.4 + 1.8, respectively) in patients with CNS involvement compared to those without [27].

Central nervous system infections

Besides the above neurological complications, infectious complications involving the CNS have also been reported. These are much rarer with only case reports in the literature. *Clostridium septicum* infection is a very serious complication that in most reported cases is fatal [37–41]. There are two case reports of favorable outcomes in children with brain abscesses caused by *C. septicum* as a complication STEC HUS [40, 42]. Table 2 summarizes the case report findings of CNS infections with *C. septicum* in STEC HUS.

Microvascular thrombosis causes necrosis of the colonic tissue that in turn damages the integrity of the colonic mucosal wall resulting in the spread of bacteria into the bloodstream in the described cases. While *C. septicum* is considered normal gut flora, germination of the *Clostridium* spores and their spread into the bloodstream and other organs occur in the setting of a low pH and low oxygen concentration found in necrotic bowel tissue [37, 42].

Gastrointestinal complications

Intestinal involvement

Diarrhea, which usually becomes bloody, is common in the prodromal phase of STEC HUS. The diarrhea may continue past the prodromal phase and persist after HUS is diagnosed. In the acute setting, GI involvement due to TMA can manifest as persistent grossly bloody diarrhea along with abdominal pain and/or distension and, in severe cases, can progress to bowel ischemia, necrosis, and perforation [43, 44]. In such patients, radiographical abnormalities such as thickened and dilated bowel loops, abnormal gas patterns, and/or free air in the peritoneum may be seen [43]. Complications such as pseudomembranous colitis and toxic megacolon have also been reported [45]. Gastrointestinal complications may be severe enough to warrant surgical intervention including partial or complete colectomy/bowel resection [43]. According to one study, the segments of the bowel most frequently involved in order of decreasing frequency are transverse colon, ascending colon, descending colon, distal ileum, and sigmoid colon with rare involvement of the rectum [43].

In a study evaluating intestinal damage from enterohemorrhagic *E. coli* infection, sigmoid tissue was obtained from two children who underwent partial sigmoidectomy due to colonic perforation [46]. Figure 3 demonstrates microscopy findings in the two patients. Areas of edema, necrosis, and hemorrhage are evident in both patients. For comparison, Fig. 3d shows normal colonic mucosa. TUNEL-positive cells were noted in all layers of the sigmoid tissue obtained from both patients confirming intestinal cell death [46].

A red appearance of the anal and perianal skin, as noted in Fig. 4, along with anal dilation, and alternating relaxation and contraction of the anal sphincter was described in three female patients who were younger than age 3 [47]. In these patients, the anal mucosa was visible and noted to have a bluish discoloration presumably due to venous congestion [47]. Rectal prolapse is another rare complication that occurs in the acute phase of HUS. In a study of 37 children with STEC HUS, three were reported to have rectal prolapse [45]. In another retrospective review of 76 children with HUS presenting to single center, rectal prolapse was observed in ten children [48].

There are several case reports of colonic stricture formation in children after recovery from HUS [49, 50]. Strictures are typically diagnosed a few months to as long as a few years after the initial presentation of HUS when the patient presents with abdominal distension, emesis and, in some settings, poor weight gain. Masumoto et al. report stricture formation in a 5-year-old Japanese girl 2.5 months after initial presentation with STEC HUS [50]. The patient underwent imaging due to constipation and abdominal pain, and X-ray further evaluation revealed a distended transverse and descending colon [50]. A contrast study confirmed a severe stricture shown in Fig. 5. At the time of surgery, the stricture along with an adhesive band was found (Fig. 6) requiring bowel resection [50].

Gallstone formation

Other GI complications include rare case reports of pigmented gallstone formation several months after the acute episode of HUS [51, 52]. Kejariwal reports a case of a 15-year-old girl who developed STEC HUS and required one blood transfusion but did not require dialysis [51]. She presented 4 months after the episode of STEC HUS with colicky right upper quadrant abdominal pain and, on ultrasound, was noted to have a dilated common bile duct with sludge in the gallbladder [51]. After initial conservative management, she presented again 2 months later with right upper quadrant abdominal pain due to gallstones and required a laparoscopic cholecystectomy [51].

Table 2 *Clostridium septicum* infections of the central nervous system (CNS) in children with Shiga toxin-producing *Escherichia coli* (STEC HUS)

Reference	Age	Clinical presentation	CNS findings	Other clinical findings	Intervention/outcome
Chiang et al. [43]	2 years	Facial twitching	CT + MRI: two abscesses in left frontal and left frontoparietal lobes noted	On HD, ileus	6-week course of antibiotics. Patient survived.
Riccio et al. [38]	16 months	Focal seizures progressing to generalized seizures	Autopsy: lateral hemisphere hemorrhage, cerebritis, and gas formation in CNS tissue	Hypotension, rash over lower abdomen spreading to flanks, cardiac arrest. Died before initiation of dialysis	Patient died.
Randall et al. [39]	4 years	Comatose, decerebrate posturing, retinal hemorrhages	CT: diffuse pneumocephalus on CT, gas in the left lateral ventricle, cerebral veins, and dural sinuses Autopsy: gas in brain tissue, edema, and TMA	On PD	Patient died.
Engen et al. [40]	3 years	Unresponsive with fixed and dilated left pupil	CT: large multifocal parenchymal hemorrhages, uncal herniation Autopsy: necrosis, pneumocephalus	Shock, multiorgan failure	Patient died.
Williams et al. [41]	2.5 years	Drowsiness, hypertonicity	MRI: bilateral hemorrhagic/ischemic lesions in temporoparietal regions that demonstrated expansion and edema on repeat MRI. Aspirate from lesions grew *C. septicum*	PD and HD	7-month course of antibiotics and aspirations. Subsequent excision of the lesions led to complete resolution. Patient survived.
Martin et al. [42]	2 years	Fixed and dilated pupils	CT: left frontal subcortical white matter edema, left frontal gyral hyperdensity, pneumocephalus uncal herniation Autopsy: parenchymal hemorrhage, necrosis, *C. septicum* present in tissue		Patient died.

PD peritoneal dialysis, *HD* hemodialysis, *MRI* magnetic resonance imaging, *CT* computed tomography

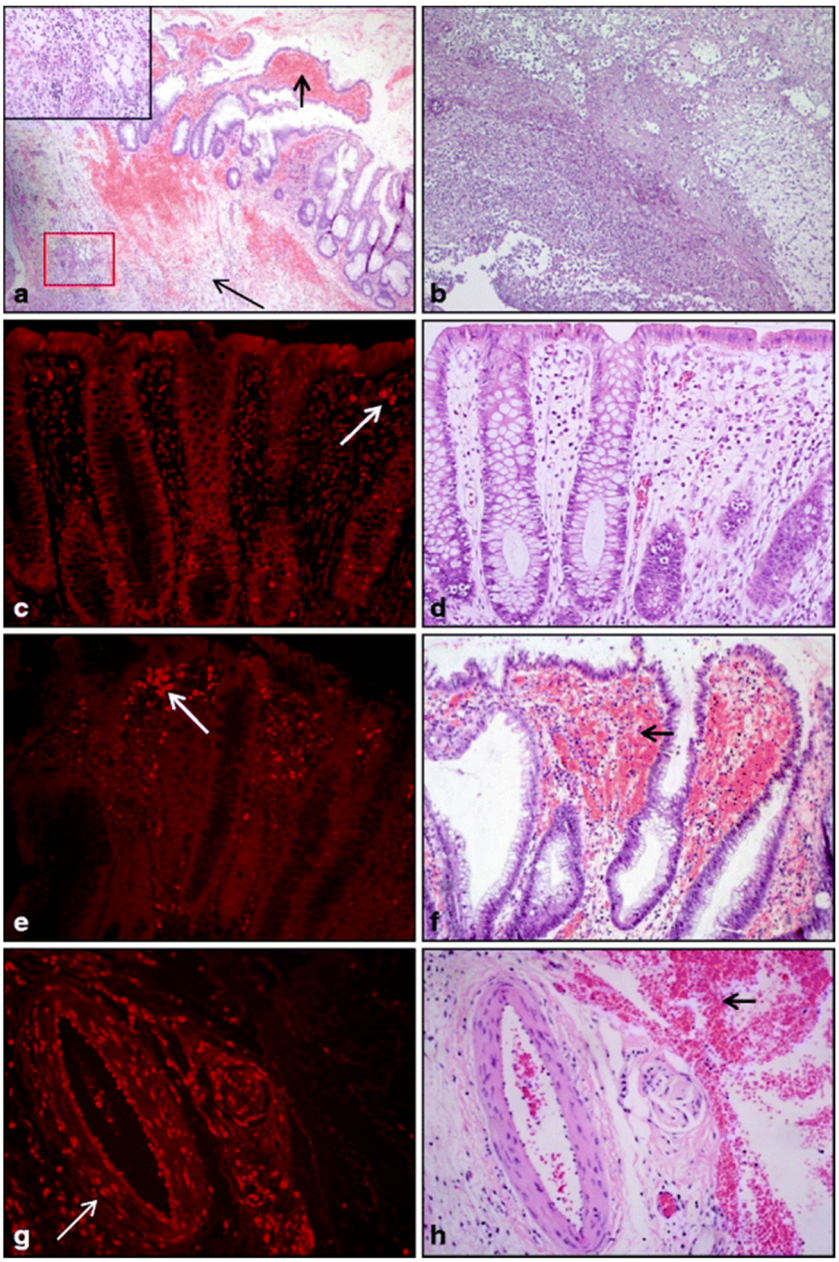

Fig. 3 Intestinal pathology in patients with STEC HUS. Pathology is from the sigmoid colon that was partly removed from two patients. **a**, **f**, **h** Light microscopy from patient 1 and **b** sigmoid colon from patient 2 (hematoxylin–eosin staining). Patient tissues exhibited hemorrhages (*short arrows*), edema (*long arrow*), inflammatory infiltrates (the area in the red box at the lower left of **a** is enlarged in the inset), and necrosis in the colonic submucosa (visible in **b**). **d** Light microscopy from control 1 stained with hematoxylin–eosin. **c**, **e**, **g** Terminal deoxynucleotide transferase-mediated dUTP nick-end labeling (TUNEL) in tissue from patient 1 (**e**, **g**) and control 1 (**c**). Abundant TUNEL labeling was detected in the lamina propria (**e**, see *arrow*) and in blood vessels (**g**, see *arrow*). Few TUNEL-positive cells were noted in the normal colonic mucosa (**c**, see *arrow*). Magnification ×50 (**a**), ×200 (**b**–**f**), ×400 (**g**, **h**). Reprinted with permission from Bekassy et al. [46]

Hepatic involvement

Elevation of bilirubin may occur due to hemolysis and some children may even present with signs of jaundice at presentation such as scleral icterus [48]. Hepatic enzyme elevation is most likely a consequence of TMA involving the liver vasculature. In a retrospective review of 76 children with HUS presenting to a single center, Grodinsky et al. observed indirect hyperbilirubinemia in 23 of 47 children [48]. Hepatic enzyme elevation was found in 25 out of 43 patients; however, a fivefold elevation from the normal range was observed in only six children [48]. None of the children with hepatic enzyme elevation developed hepatic failure or chronic hepatitis [48].

Pancreatic complications

Amylase and lipase elevation is also commonly encountered in children with STEC HUS during the acute phase. A rise in plasma pancreatic enzymes was noted in as many as 66% of the children having STEC HUS [48]. However, it is important to note that both amylase and lipase are partially cleared by the kidney; hence, in the setting of renal failure, their serum levels are elevated. Pancreatitis should be suspected based on clinical symptoms of pancreatitis and not exclusively based on an elevated amylase and lipase. Mild pancreatitis is typically managed conservatively and resolves on its own over the course of the illness. Ultrasound of the pancreas can

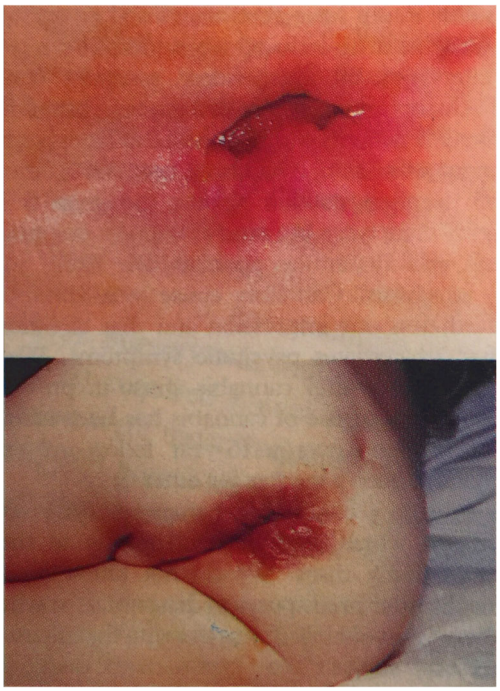

Fig. 4 Perianal and anal findings in two patients with hemolytic uremic syndrome. Reprinted with permission from Vickers et al. [47]

show pancreatic edema, and very rarely, the pancreas can show total necrosis with calcifications in the late phase of HUS [53, 54]. Ashraf et al. report a case of a 2-year-old child with STEC HUS who developed pancreatitis with significantly elevated amylase and lipase followed by

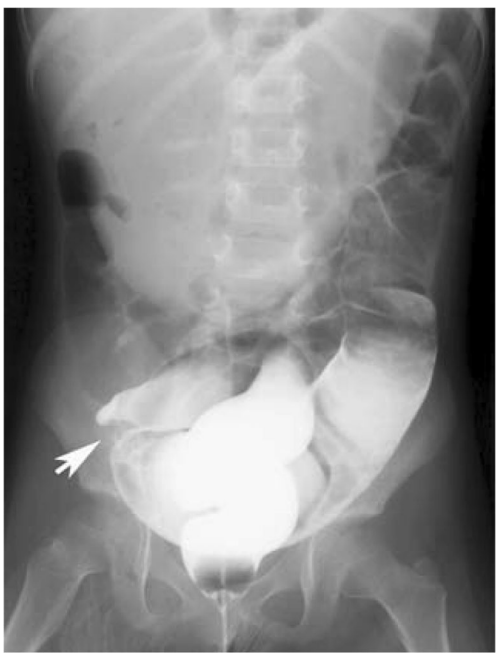

Fig. 5 Colonic stricture noted (white arrow) on a contrast study of the colon. Reprinted with permission from Masumoto et al. [50]

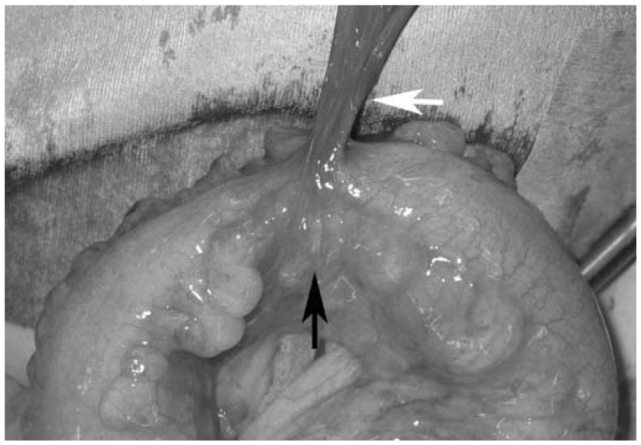

Fig. 6 Operative photograph of the above colonic stricture (black arrow) identified by the contrast study. Adhesive band is attached to the stricture (white arrow). Reprinted with permission from Masumoto et al. [50]

hyperglycemia [55]. An abdominal CT, shown in Figs. 7 and 8, confirmed an enlarged pancreas with findings suggestive of pancreatic necrosis [55]. The child had persistent exocrine and endocrine deficiency of the pancreas on follow-up at 1 year and a repeat CT showed an atrophic pancreas [55].

The development of insulin-dependent diabetes mellitus (IDDM) during an episode of STEC HUS has been well documented and can occur both in the acute and long-term setting. Pancreatic islet cell involvement was first described in 1984 and subsequently has been well established. The pathophysiology of the diabetes is believed to be impairment in pancreatic function due to thrombi formation in the pancreatic microvasculature resulting in necrosis of the pancreatic islet cells. This in turn results in impaired endocrine function of the pancreas leading to low insulin production. An inadequate rise in insulin in the setting of hyperglycemia has been observed in

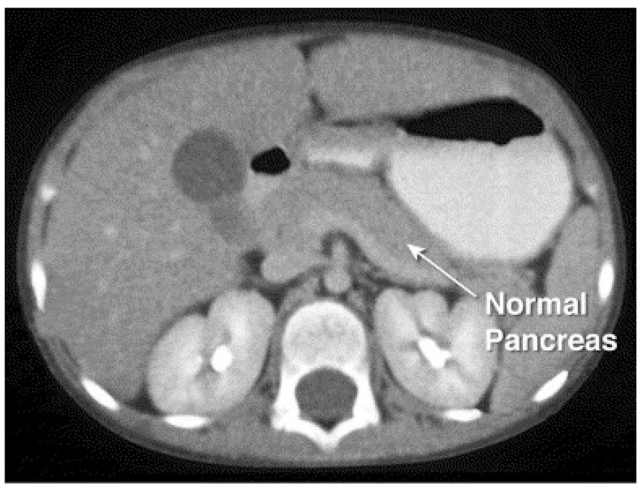

Fig. 7 Abdominal CT showing normal contrast enhancement of the pancreas. Reprinted with permission from[55]

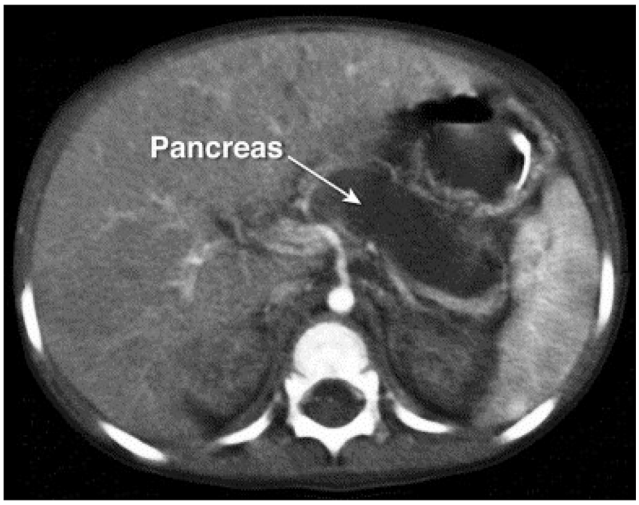

Fig. 8 Abdominal CT showing enlarged pancreas and findings consistent with pancreatic necrosis. Reprinted with permission from Ashraf et al. [55]

some patients. The mechanism for the IDDM is not due to antibody-mediated damage to islet cells because antibodies to islet cell cytoplasm, surface antigens, and insulin have not been detected [56, 57]. Autopsy findings in affected patients reveal TMA that may selectively involve the islets of Langerhans or diffusely involve both the exocrine and endocrine pancreas [15, 53, 54]. Generalized pancreatic inflammation without TMA and massive pancreatic hemorrhage in rare cases have also been observed [15, 54].

Tapper et al. found that 8% (3/37) of children with STEC HUS developed glucose intolerance in the acute setting [45]. In another study by Robson et al., hyperglycemia was found in 6.6% of the study patients (8/121) [58]. Seven of the eight patients required treatment with insulin for glucose management, and the average duration of insulin treatment was 18 days (range 1–46 days) [58]. Suri et al. performed a meta-analysis and noted that the pooled incidence of IDDM during the acute phase of HUS is 3.2% [59]. IDDM occurred more in children with severe disease, and these children also suffered from a higher mortality of 23% compared to the children who did not develop IDDM [59]. In the meta-analysis, 49 children developed IDDM and all except one child developed IDDM in the first 14 days of presentation [59]. In one case, hyperglycemia was noted prior to the initiation of peritoneal dialysis [59]. Two children who recovered from the acute episode of HUS with the development of IDDM presented at later times with IDDM between 3 and 60 months [59]. Of the 49 children, 34 survived and 11 children had IDDM from the onset of the acute illness. The remaining 21 children reportedly had complete recovery, but it is important to note that the follow-up in these children was less than 12 months, and in a significant percentage of these patients, follow-up was altogether missing [59]. Later onset of IDDM has been well described in children who have suffered from STEC HUS. Nesmith et al. report a case of a 2-year-old boy who developed IDDM 11 years after the episode of HUS [60]. Pena et al. describe two children who developed diabetes 8 years after an episode of presumed diarrhea-associated HUS [61]. Both children had also required insulin during the acute phase of HUS but had been able to come off the insulin shortly thereafter [61]. Casteels et al. report a case of a 12-year-old boy who had diarrhea-positive HUS at age 6 and developed hyperglycemia requiring insulin for 21 days [62]. He then presented 6.8 years later with IDDM [62].

Cardiovascular complications

Cardiovascular involvement presenting as hypertension, congestive heart failure, pericardial effusion, depressed myocardial function, and left ventricular hypertrophy has been well described in children with STEC HUS. Hypertension occurs commonly and is due to a constellation of conditions including volume overload and electrolyte imbalance in the setting of underlying TMA involving the kidneys. The incidence of hypertension in HUS reported by Brandt et al. was 27% during the admission (defined by BP > 95 percentile) and, in the most recent outbreak of *E. coli* O104:H4 in Germany, was noted to be about 33% at the time of presentation (defined by a BP > 90 percentile) [2].

Brandt et al. retrospectively reviewed 37 children who developed STEC HUS due to an outbreak of *E. coli* 0157:H7 in 1993 and noted cardiovascular complications in 13 of the 37 patients, out of which ten children had hypertension as defined by a blood pressure greater than the 95 percentile [63]. Five of the 13 patients had pericardial effusions and four had depressed myocardial function [63]. Three patients died out of which one patient had multisystem organ failure including coma, depressed myocardial function, and acute respiratory distress syndrome [63]. The second child had myocardial failure and shock at the time of death. Both these patients also had massive colonic necrosis requiring total colectomies [63].

There are several case reports of children with STEC HUS who develop depressed left ventricular (LV) function with suspected myocardial ischemia and an associated rise in biomarkers along with rare reports of myocarditis and cardiac tamponade [28–32, 64, 65]. It is not entirely clear what causes the pericardial fluid collection or myocardial inflammation in the patients described.

Please refer to Table 3 for a summary of relevant case reports.

On autopsy of 64 patients who died with STEC HUS, 19 had cardiac involvement out of which 15 patients had TMA in the myocardial vessels, two had multiple hemorrhages and necrotic foci without TMA,

Table 3 Relevant case reports of cardiovascular complications in Shiga toxin-producing *Escherichia coli* (STEC HUS)

Reference	Age	Clinical presentation	Cardiac imaging findings	Other clinical findings	Intervention/outcome
Askiti et al. [28]	22 months	Circulatory collapse on day 6 of hospitalization	ECHO showed diminished LV function with EF of 18%	Elevated troponin I during the event	Normalization of cardiac function after 4 days
Thayu et al. [29]	9 years	New onset oxygen requirement on day 11 of illness	ECHO showed mildly decreased LV compliance and small apical pericardial effusion	Elevated troponin I during the event	Not discussed in the report
Andersen et al. [30]	12 years	Cardiac arrest twice on day 3 of admission	ECHO showed < 10% EF	Elevated troponin T, CK	Cardiopulmonary bypass circuit set up for 10 days. ECHO normal by day 10
Abu-Arafeh et al. [31]	13 years	Circulatory collapse on day of hospitalization	EKG: sinus bradycardia	Autopsy confirmed myocarditis	Patient died
Birk et al. [32]	6 years	Circulatory collapse	Not performed	Autopsy showed pericardial fluid collection and myocardial necrosis with neutrophilic infiltrate	Patient died
Mohammed et al. [33]	2 years	Hypotension requiring ionotropic support of day 6 of hospitalization	ECHO showed paradoxical movement of right atrium suggestive of tamponade and low EF of 56%	Elevated CK and troponin I	Pericardiocentesis with pericardial drain placement

LV left ventricular, *EF* ejection fraction, *CK* creatinine kinase, *ECHO* echocardiogram, *EKG* electrocardiogram

and two patients had grossly visible areas of infarction in the left ventricular wall [15]. Myocarditis has been described as the cause of death in a case report and pathology findings as shown in Fig. 9 [30].

Rare case reports

Ocular involvement

There are rare case reports of ocular involvement with STEC HUS, which can manifest as retinal hemorrhages and ischemic lesions along the optic nerve secondary to TMA (Fig. 10) [33, 34].

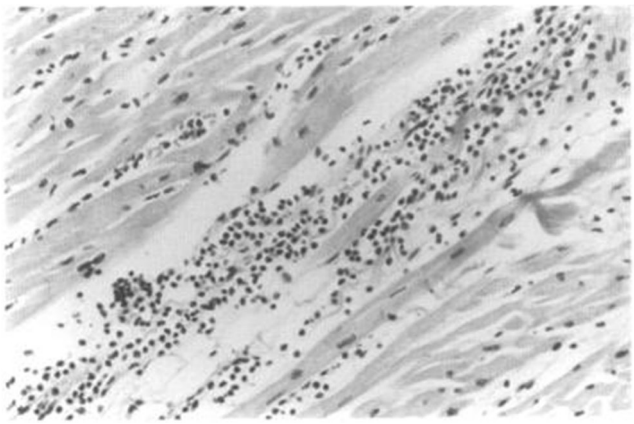

Fig. 9 Focal inflammatory cell infiltration in the myocardium. Reprinted with permission from Abu-Arafeh et al. [30]

Rhabdomyolysis

There are also case reports of rhabdomyolysis associated with HUS with the patients complaining of progressive muscle weakness and tenderness [35, 36]. Figure 11 shows muscle

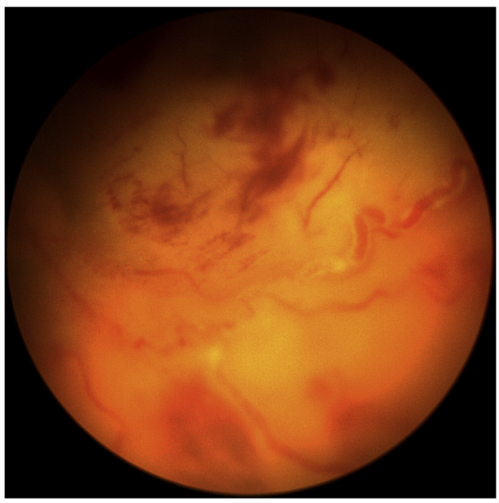

Fig. 10 Fundoscopic evaluation of the retina showing scattered retinal hemorrhages. Reprinted with permission from Loudon et al. [33]

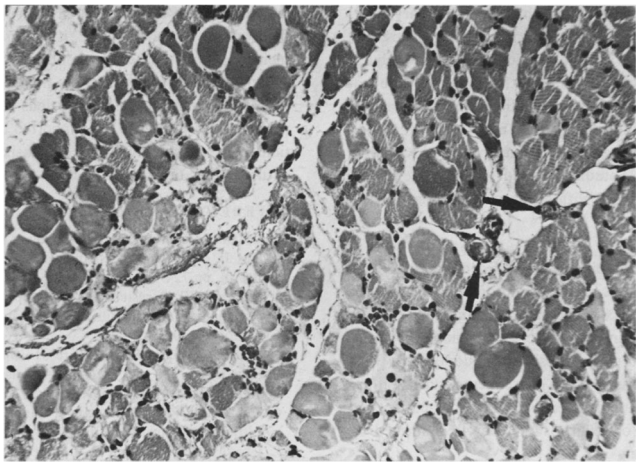

Fig. 11 Light micrograph of muscle biopsy demonstrating severe segmental rhabdomyolysis and fibrin thrombi (arrows) in microvasculature. Reprinted with permission from Andreoli and Bergstein [35]

biopsy findings in an affected child who went on to recover from the illness [35].

Conclusion

STEC HUS is a common cause of acute kidney injury in children with as many as half of affected children requiring dialysis. It can have significant extrarenal involvement in the acute and chronic setting. Children hospitalized with STEC HUS should have close monitoring of their neurological status. Elevated serum glucose should raise suspicion for the development of diabetes mellitus, and hemodynamic instability should raise concern for cardiac involvement. Bowel ischemia/perforation may occur, and in this setting, the patient will develop severe abdominal pain and signs of an acute abdomen. Ocular involvement and rhabdomyolysis are rare. Long-term complications include renal impairment that may present as hypertension, proteinuria, and a low GFR. Long-term extrarenal complications include bowel strictures, gallstones, IDDM, and residual neurological impairment. Supportive therapy still remains the mainstay of treatment.

Key points

1. Neurological involvement in STEC HUS is associated with a higher mortality.
2. The risk of bowel necrosis and perforation may necessitate surgical intervention.
3. Elevated amylase and lipase are insufficient for making the diagnosis of pancreatitis. Clinical correlation with symptoms of pancreatitis should be made.
4. Hyperglycemia and diabetes mellitus may develop in the acute setting or several months after the acute HUS presentation.
5. Cardiac dysfunction may occur in children with STEC HUS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Multiple-choice questions (answers are provided following the reference list)

1. The following neurological complication can occur in the setting of STEC HUS:

   a) Seizures
   b) Stroke
   c) Coma
   d) All of the above

2. Hyperglycemia in the acute setting of STEC HUS is due to:

   a) Dextrose containing dialysate solutions
   b) Stress response of the body
   c) Pancreatic involvement in STEC HUS
   d) Dextrose containing IV fluids

3. Which of the following gastrointestinal complications may occur several months after STEC HUS:

   a) Hepatitis
   b) Bowel stricture
   c) Appendicitis
   d) Meckel's diverticulum

4. The following extrarenal involvement has not been described with STEC HUS

   a) Elevated bilirubin
   b) Diabetes mellitus
   c) Pigmented gallstones
   d) Arthritis

5. Circulatory collapse occurs suddenly in a 3-year-old girl on day 2 of admission with STEC HUS. The patient is on peritoneal dialysis. One important test to order at that time is:

   a) Coombs testing
   b) Cardiac ECHO
   c) Ultrasound of the pancreas
   d) Repeat stool cultures

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Answers

1. d; 2. c; 3. b; 4. d; 5. b