HHS Public Access

Author manuscript

Pediatr Nephrol. Author manuscript; available in PMC 2021 November 27.

Published in final edited form as:

Pediatr Nephrol. 2019 August ; 34(8): 1337–1348. doi:10.1007/s00467-018-4039-7.

Extra-renal manifestations of atypical hemolytic uremic syndrome

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare and complex isease resulting from abnormal alternative complement activation with a wide range of clinical presentations. Extra-renal manifestations of aHUS can involve many organ systems, including the peripheral and central nervous, gastrointestinal, cardiovascular, integumentary, pulmonary, as well as the eye. While some of these extra-renal manifestations occur in the acute phase of aHUS, some can also occur as long-term sequelae of unopposed complement activation. Extra-renal symptoms are observed in approximately 20% of patients with aHUS, with the incidence of specific organ system complications ranging from a few case reports to 50% of described patients. Careful monitoring for extra-renal involvement is critical in patients with aHUS, as prompt evaluation and management may decrease the risk of high morbidity and mortality associated with aHUS.

Keywords

atypical hemolytic-uremic syndrome (aHUS); thrombotic microangiopathy (TMA); extra-renal manifestations; gastrointestinal complications; cardiovascular complications; neurologic complications

Introduction:

Hemolytic uremic syndrome (HUS) is a rare disorder that occurs in both children and adults, and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal dysfunction. Traditionally, HUS has been divided into diarrhea-positive and diarrhea-negative subtypes. The former, also referred to as Shiga toxin positive HUS, is usually mediated by Shiga-like toxin producing *Escherichia coli* (STEC) serotype 0157:H7 and less commonly Shiga toxin producing *Shigella dysenteriae type 1* [1]. All other cases of HUS have traditionally been referred to as atypical or diarrhea-negative HUS. Atypical HUS (aHUS) comprises approximately 10% of HUS cases in children [2]. Although not well established, the estimated annual incidence of aHUS in the United States is one in 500,000 individuals and seven in 1,000,000 individuals in Europe [1, 3]. While aHUS

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Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest

often resembles Shiga toxin positive HUS clinically, research has revealed that aHUS is a group of disorders resulting from overactivation of the alternative complement pathway. Approximately 40–60% of patients diagnosed with aHUS have identifiable pathogenic gene mutations of the alternative complement factors, leading to a loss-of-function mutation of a regulatory gene, including CFH, CFI, or CD46, or a gain-of-function mutation in an effector gene, such as CFB, C3, or THBD [4–6]. Furthermore, autoantibodies to complement proteins are responsible for up to 10 percent of aHUS cases. Under physiologic conditions, the alternative complement pathway is continuously active at low levels and becomes amplified under conditions of infection or endothelial cell stress or damage. The proposed mechanism for development of aHUS is a trigger event, such as infection, pregnancy, medications, malignancy, organ transplantation, or a systemic illness that initiates inflammatory reaction and the release of inflammatory mediators causing endothelial cell damage and exposure of subendothelial matrix. Patients with dysregulation of the alternative complement pathway cannot efficiently restrict complement activation. This state allows uncontrolled and chronic complement activity on multiple physiologic pathways leading to propagation of endothelial cell damage and development of thrombotic microangiopathy (TMA) with subsequent devastating clinical consequences leading to end-organ damage or failure [7–10]. A potent proinflammatory mediator, C5a is proposed as a key link between the inflammatory and fibrotic pathways [11]. Additionally, the C5b-9 membrane attack complex (MAC) leads to activation of platelets, leukocytes, and endothelial cells and further activation of the alternative complement pathway via the positive feedback loop [12, 13].

Although the renal microvasculature is a common site of TMA, aHUS can manifest in many organ systems and can mimic many conditions [12, 14]. Several hypotheses, recently reviewed by Hofer et al, have been proposed to explain the organ-specific susceptibility to TMA [15]. The high predisposition of renal microvasculature results from higher susceptibility to complement activation and dysregulation by fenestrated architecture of the glomerular endothelial cells, lack of surface bound complement regulators at the glomerular basement membrane, and exquisite dependence of glomerular endothelial cells on vascular endothelial growth factor (VEGF). Although the hypotheses suggest that the organ-specific manifestations of TMA are determined by the specific anatomy of the endothelial cells, as well as the quality and quantity of factors modulating the endothelial cell, these hypotheses still await experimental validation.

Because of the high morbidity and mortality associated with aHUS, it is crucial to have an understanding of the potential extra-renal manifestations of the disease and its associated laboratory findings, in order to ensure prompt diagnosis and treatment. The primary triad of laboratory findings includes hemolytic anemia with a hemoglobin level usually less than 8 g/dL, thrombocytopenia or an unexplained fall in platelet count, and evidence of renal dysfunction, including an elevated serum creatinine level for height and age, hematuria and/or proteinuria. Evidence of microangiopathic hemolytic anemia should be confirmed with a peripheral blood smear showing schistocytes and helmet cells, along with other laboratory studies consistent with hemolytic anemia including an elevated serum lactate dehydrogenase (LDH) level and a low serum haptoglobin concentration. A Coombs' Test should be obtained to evaluate for autoimmune hemolytic anemia, and will be negative in cases of aHUS [2]. Abnormal complement levels can be seen, including low levels

of C3, C4, CFH, CFI, CFB and CD46, along with elevated levels of C3d, C5a and soluble C5b-9 [4, 5, 16, 17]. While diarrhea is classically associated with the clinical prodrome of Shiga toxin positive HUS, diarrhea is observed in approximately 50% [18–20] of patients proceeding or during the acute phase of aHUS. As such, stool studies in patients with and without diarrhea should be negative for STEC. Genetic testing for known complement mutations should be obtained in all patients with suspected aHUS. In the clinically appropriate setting, testing for automimmune and connective tissues disorders including systemic lupus erythematosus (SLE), antiphospholipid syndrome and systemic sclerosis should be considered.

Eculizumab, a monoclonal humanized antibody directed against C5, is the mainstay of treatment for aHUS. By preventing the cleavage of C5 and the subsequent formation of MAC, eculizumab inhibits activation of the terminal complement cascade and complement driven epithelial damage leading to TMA. Prior to the development of eculizumab, treatment options for aHUS included plasma therapy, dialysis and kidney transplantation, however aHUS recurrence following discontinuation of therapy or kidney transplantation was frequently observed [16].

In this review we will discuss the broad range of extra-renal manifestations seen in aHUS. Overlapping clinical symptoms with other forms of TMA including Shiga toxin positive HUS, thrombotic thrombocytopenic purpura (TTP) and HELLP syndrome commonly occur. TMA can also occur in the setting on autoimmune and connective tissues disorders, and cases of aHUS associated with antiphospholipid syndrome have been reported [21]. High clinical suspicion is therefore required to promptly diagnose patients and reduce the morbidity and mortality associated with aHUS.

Neurologic Manifestations of aHUS:

Neurologic symptoms are the most common extra-renal manifestation occurring in aHUS, with symptoms reported in 8 to 48% of cases [6, 17–19, 22, 23]. In a recent study of the national Turkish pediatric aHUS registry [24], central nervous system involvement was reported in 27.2% of subjects. The most common symptoms included seizures, vision loss, hemiparesis, headache, altered consciousness, hallucinations and encephalopathy. Other reported neurologic manifestations include confusion, agitation, decreased reflexes, nystagmus, diplopia, hemiplegia, focal neurologic deficits and coma [6, 17, 19, 25–27].

Seizures can occur during the acute phase of aHUS, both in the presence and absence of hypertension. In a cohort of 23 patients with diarrhea-negative HUS described by Neuhaus et al. [22], 11 patients (48%) had cerebral convulsions. Of the 11 patients, 6 had elevated blood pressure. In the registry of Turkish pediatric aHUS patients [24], 20.7% of patients were reported to have seizures and 50% of patients with CNS manifestations had documented hypertension. Of those with CNS symptoms, abnormal radiographic findings were demonstrated in 18 of 34 patients who had undergone neurologic imaging. Of the 18 patients, 5 patients had signal changes consistent with hypertension and posterior reversible encephalopathy syndrome. The remaining 13 patients had MRI changes secondary to TMA, including bilateral and symmetric hyper intensity lesions of the basal ganglia, cerebral

peduncles, caudate nuclei, putamen, thalami, hippocampi, insulae, brainstem and deep white matter [24].

Findings on cerebral imaging associated with TMA can be diverse, and can involve changes in the posterior white matter, posterior cortex, deep white matter, thalami, brainstem and basal ganglia [26, 28]. Gulleroglu et al. [26] reported two cases of pediatric patients with aHUS, significant neurologic symptoms and abnormal MRI findings. Case 1 was an 11-year-old female with aHUS, who experienced multiple tonic-clonic seizures one month after initial presentation, while receiving plasma exchange therapy. Genetic testing confirmed two polymorphisms in the *CFH* gene in exon 7 and exon 9, and two compound heterozygote mutations in complement factor I of unknown significance. The patient subsequently developed confusion and loss of vision. Vitals were notable for normal blood pressure. Magnetic resonance imaging (MRI) showed increased signal in the occipital and posterior parietal lobes on T-2 weighted and fluid attenuated inversion recovery (FLAIR) imaging. Edema was also present on diffusion weighted MRI. Following treatment with eculizumab the patient demonstrated complete recovery on neurologic exam and imaging. The second patient was a 6-year-old female [26] who presented with vomiting and abdominal pain. Her symptoms progressed to include anuria, pallor and weakness. Laboratory studies were as follows; hemoglobin 10.3 g/dl, platelets 51,000/ul, serum creatinine 4.67 mg/dl, LDH 1590 U/l, haptoglobin 6 mg/dl, C3 5 mg/dl (normal 79–152 mg/dl), schistocytes on peripheral smear and negative STEC and *Shigella dysenteriae* type 1. Six days after presentation the patient developed a tonic-clonic seizure, along with nystagmus and vision loss. The patient was normotensive on exam. MRI showed hyperintense white matter lesions in the bilateral posterior parietal and occipital lobes. The patient's neurologic exam returned to normal following treatment with eculizumab.

In many cases, neurologic symptoms improve rapidly after initiation of treatment with eculizumab [1, 25, 26]. In five adult patients with aHUS reported by Tsai et al. [29], all five presented with altered mental status; neurologic symptoms including confusion, headache, somnolence and scotomas. Four of the five patients had resolution of their neurologic manifestations at day 7 following treatment with eculizumab. Another patient, an 8-year-old male with anti-Factor H antibody associated aHUS, was presented by Diamante et al. [25]. The patient developed vomiting, altered consciousness and decreased reflexes one week after admission to the hospital. Cerebral MRI showed multifocal hyperintensities located in the bilateral cerebellum, subcortical parietal and left frontal lobes, consistent with ischemic injury. Following the second treatment with eculizumab the patient's psycho-cognitive function fully recovered. Repeat imaging showed regression of the cerebellar and frontal lobe lesions three months after discharge from the hospital.

As described, neurologic involvement occurs frequently in aHUS, and has a wide range of clinical manifestations. For this reason, the presence of neurologic findings cannot be used to disguising aHUS from other forms of TMA, including thrombotic thrombocytopenic purpura (TTP). While aHUS is mediated by complement dysregulation, TTP is caused by a deficiency in ADAMTS13 activity. ADAMTS13 activity is generally less than 10% in patients with TTP. This decreased activity can be secondary to a loss of protein function or the presence of anti-ADAMTS13 antibodies [16]. TTP and aHUS are distinctly

different clinical entities, and should be distinguished from one another in order to provide appropriate therapy. A variety of inciting factors should also be considered when evaluating neurological symptoms, including uremia, electrolyte derangements, hypertension, ischemia, and cerebral edema. Careful attention to urea reduction rate, electrolyte correction, blood pressure control and management of increased intracranial pressure should be made to reduce the risk of long-term neurologic complications.

Given the diversity of clinical symptoms and the array of findings on cerebral imaging seen in aHUS, some neurological manifestations appear to result from direct involvement of the central nervous system vasculature, while others appear to be secondary to aHUS complications. While some MRI findings can help distinguish between thrombotic microangiopathic lesions and hypertensive complications [28], more research and detailed accounts of patients with neurologic manifestations in aHUS is required to further knowledge in this area. A better understanding of diagnostic testing that may help distinguish various causes of neurologic symptoms will allow practitioners to provide better treatment and counseling to patients and families living with aHUS.

Cardiac and Central Vascular Manifestations of aHUS:

Microangiopathy and endothelial damage secondary to increased activation of C5 and MAC formation is central to the pathogenesis of aHUS. Endothelial damage leads to thrombus formation, platelet consumptions and red cell sheering. This thrombotic microangiopathic process leads to renal dysfunction, thrombocytopenia and hemolytic anemia [17]. While the renal microvasculature is often the primary area of TMA involvement, cardiovascular complications involving both small to large vessel injury have been described.

The incidence of cardiovascular complications has been reported as 3–10% in patients with aHUS [19, 30]. In the review of 169 pediatric patients with aHUS in Turkey, cardiac manifestations were identified in 7% of children [24]. Complications included left ventricular hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, elevated CK-MB level, valve insufficiency, intra-cardiac thrombus and tachycardia.

While cardiac dysfunction may be associated with hypertension and fluid overload secondary to acute kidney injury in some patients with aHUS, cardiac symptoms can occur independent of these factors suggesting direct injury to the myocardial tissue and vasculature [31]. Microangiopathic injury in the coronary vessels can lead to small vessel wall thickening and subendothelial swelling, placing patients at risk for severe cardiac dysfunction and sudden cardiac death [32]. The clinical course of a 19-month-old female with significant cardiac dysfunction from aHUS was reported by Hu et al. [33]. The girl presented to her local hospital with five days of vomiting, non-bloody diarrhea and decreased urine output. Serum studies showed a hemoglobin of 8.5 g/dl, platelets 26×10^9/l, fragmented red blood cells on peripheral smear, LDH 4,993 IU/l, negative direct coombs test, creatinine 294 umol/l, and low C3 and C4 levels at 0.69 g/dl and 0.13 g/l respectively. On arrival the patient was normotensive and non-edematous. Shortly after admission she had a decline in her mental status and experienced a generalized tonic-clonic seizure. Due to her early CNS involvement, there was high suspicion for aHUS and treatment with

eculizumab was initiated on the first day of the hospitalization. The patient was started on continuous venovenous hemofiltration, which was quickly transitioned to peritoneal dialysis. Stool studies were negative for STEC and ADAMTS13 activity was 94%. On day 5, the patient became hypotensive and tachycardic, and physical examination was notable for an enlarged liver. An echocardiogram revealed dilated cardiomyopathy with an ejection fraction of 30%. She was continued on Eculizumab therapy and follow-up echocardiograms showed improvement in her cardiac function, with normal biventricular function by day 15 of her hospitalization. Follow-up genetic testing showed a rare variant in the Factor H gene of unknown significance.

Additional evidence of direct myocardial injury was presented by Sallee et al. [32], who described a 43-year-old female patient with aHUS secondary to a *CFH* gene mutation, who died of sudden cardiac arrest 15 days after initial presentation. On admission, the patient had nausea, headache and dyspnea. Peripheral edema was present and vitals were notable for an elevated blood pressure of 180/90 mmHg. Further evaluation was consistent with TMA. The patient was started on dialysis and plasma exchange. On day 15 the patient had circulatory arrest. Echocardiogram was notable for a pericardial effusion with tamponade physiology. Despite resuscitative measures the patient died. Autopsy showed a myocardial infarction without obstruction of the coronary vessels. Small vessel wall thickening and subendothelial swelling was appreciated on pathologic examination; however, coronary thrombi and atherosclerotic lesions were absent. Staining for MAC was positive in the small coronary vessels and infarcted myocardial tissue.

Direct involvement of large arterial vessels has also been demonstrated in patients with aHUS. A small number of case reports of critical steno-occlusive arterial disease have been described in pediatric patient with aHUS on chronic hemodialysis. Loirat et al. [34] described a pediatric patient with extensive and potentially life threating large vessel arterial stenoses associated with aHUS. The female patient was diagnosed with aHUS in infancy and genetic testing was notable for a heterozygous gain of function mutation in the *CFB* gene. The patient was on chronic hemodialysis, after failed renal transplant at 19 months of age. At the age of 10, she began to experience intermittent hemiparesis and loss of consciousness with drops in blood pressure below 90/50 during intermittent hemodialysis. Angiography showed stenoses of the cerebral, vertebral, carotid and subclavian arteries. Additional imaging at the age of 12 revealed pulmonary, coronary, splenic, humeral and celiac artery stenoses. No calcifications or evidence of atherosclerosis was appreciated on imaging or on interventional cardiac catheterization. At the age of 13, her vascular stenoses had worsened on follow-up studies. The patient later died due to complications following attempted carotid angioplasty. A second patient, a 15-year-old female [35, 36] with ESRD secondary to aHUS from a familial *CFH* gene mutation, developed intermittent sensory motor symptoms while receiving hemodialysis. After failure of two renal allografts secondary to aHUS recurrence at the ages of 5 and 12, the patient had returned to chronic hemodialysis treatment. The onset of neurologic symptoms correlated with decreased blood pressure while on hemodialysis. Magnetic resonance angiography (MRA) revealed severe stenosis of the anterior and middle cerebral arteries. No evidence of calcifications or atherosclerosis was identified on imaging [36]. The patient received a third renal transplant at the age of seventeen. Following transplant, she sustained frontal and frontoparietal brain

infracts with associated hemiparesis, seizures and altered mentation. She was maintained on twice weekly plasma exchanged until four months post-transplant when treatments were reduced to once per week. She subsequently developed aHUS recurrence with rapid decline in renal function, along with hemolytic anemia and thrombocytopenia. She was later transitioned to treatment with eculizumab, with no additional neurologic events reported after 16 months of eculizumab therapy [37].

Large vessel steno-occlusive arterial disease associated with aHUS has also been reported in patients with normal hematologic studies. A patient with multiple identified mutations in the *CFI, CFB and CFH* genes, described by Bekassy et al. [38], presented with evidence of aHUS at 17 months of age. She developed end stage renal disease (ESRD), and underwent decreased-donor renal transplant with native nephrectomies at the age of 3. Despite plasma exchange, she developed aHUS recurrence and malignant hypertension, necessitating removal of her renal transplant at the age of 4. Following transplant nephrectomy the patient had no evidence of hemolysis or thrombocytopenia. Six years later, the patient experienced an episode of headache, vomiting, aphasia, weakness, ataxia and altered mental status concerning for a transient ischemic attack. MRA showed critical stenosis of the carotid arteries. The patient did not have left ventricular hypertrophy on echocardiogram and ophthalmologic exam did not show evidence of hypertensive retinopathy. Due to the vascular findings, additional complement testing was obtained and revealed ongoing complement activation. The patient was started on eculizumab and subsequently underwent decreased donor renal transplant without recurrence of her HUS. Follow-up vascular imaging showed no progression of the vascular lesions at one year [38]. Atherosclerotic coronary artery disease is seen in up to 38% of patients with ESRD who are starting dialysis [39]. Coronary lesions observed in this patient population frequently exhibit extensive calcification [39]. The vascular lesions identified in the patients discussed above, did not show evidence of atherosclerosis or calcifications, which are typically associated with ESRD and hemodialysis related vascular disease. These cases provide further evidence of direct large vessel vascular injury from ongoing complement activation, which may be exacerbated by chronic hemodialysis.

Cardiomyopathy has also been reported at varying frequency in patients with aHUS. In an Australian cohort [40] of patients who received eculizumab, one of ten patients was diagnosed with severe cardiomyopathy. Of the ten patients, six were reported to have cardiovascular involvement, including hypertension and cardiac failure. In an earlier report by Neuhaus et al. [22], 10 of 23 children (43%) with diarrhea negative HUS were diagnosed with cardiomyopathy. In a larger cohort of children described by Johnson et al. [23], 3 of 71 (4.2%) patients exhibited cardiomyopathy or heart failure.

A 1-year-old female [31] with aHUS and cardiomyopathy was described by Vilalta et al. Laboratory studies were notable for hemoglobin 6.5 mg/dl, platelets 108×10^9/l, creatinine 221 umol/l (normal 35–44 umol/l), LDH 2674 U/l and presence of schistocytes on peripheral blood smear. Stools cultures were negative and ADAMTS13 activity was within normal range at 83%. The patient was started on plasma exchange therapy and hemodialysis. Despite therapy two to three times per week, the patient continued to have severe anemia requiring hospitalization. The patient's status continued to worsen over the following

months. Approximately 10 weeks after initial presentation she was diagnosed with arterial hypertension and dilated cardiomyopathy. She had a cardiorespiratory arrest, after which she was successfully resuscitated. Genetic testing returned and was significant for a novel heterozygous mutation in the C-terminal region of the *CFH* gene. The patient had recurrent episodes of pulmonary edema and a decreased cardiac ejection fraction of 32% reported on imaging five months after initial presentation. At seven months, cardiac function remained depressed with an ejection fraction of 31%. Eculizumab therapy was initiated and led to normalization of blood pressure, cardiac function and renal function.

Long-term cardiac insufficiency can also occur, and can lead to a significant increased risk of morbidity and mortality patients with aHUS. In an adult patient with anti-Factor H antibody associated aHUS, death from cardiac insufficiency occurred two years after onset of clinical symptoms [18]. In a study of 57 patients with aHUS and kidney transplants, four patients died of cardiovascular events during the follow-up period; the events included acute cardiac failure, myocardial infarction and stroke [41]. Cardiovascular complications have been reported in as high as 20% of patients with *CFH* mutations [14], and increased susceptibility to cardiovascular manifestations appear to occur with anti-Factor H antibodies, as well as gain of function C3 and CFB mutations [30]. Cardiac dysfunction was reported in 8 out of 14 patients with C3 mutations described by Roumenina et al. [42]. Seven patients had dilated cardiomyopathy, two of which who had delayed onset at 2 and 6 months following hematologic remission, and the eighth patient died from a cardiac event.

Skin and Peripheral Vascular Manifestations of aHUS:

Dermatologic and peripheral vascular manifestations have been described in a small number of reported aHUS cases. Skin changes that have been described in the literature range from cutaneous rash to peripheral gangrene [43–46] (Table 1). When present in young pediatric patients, involvement of the skin and peripheral vascular system is often severe and frequently occurs as an early systemic manifestation of the disease. In some cases, skin changes can occur in the absence of anemia or thrombocytopenia, and therefore may be evidence of persistent complement activation in the absence of other biochemical abnormalities typically associated with aHUS. Skin changes and peripheral ischemia, while rare, appear to have rapid response to plasma exchange and/or eculizumab.

Ocular Manifestations of aHUS:

Ocular injury is a rare, but when present, can be a serious complication of aHUS. While central nervous system involvement occurs in 8–48% [6, 17–19, 22, 23] of patients with aHUS, ocular involvement has been described in only a small number of case reports. A study by Sturm et al. [47] in 2010 reported ocular involvement in 4% of pediatric patients with hemolytic uremic syndrome. However, of the 87 pediatric cases reviewed, all patients with documented ophthalmologic changes were diagnosed with Shiga toxin positive HUS.

Acute ocular symptoms include decreased visual acuity [48, 49], visual scotomas [29], ocular pain, diplopia [48] and blurred vision [50]. Visual symptoms frequently have sudden onset, and can lead to near or complete loss of vision [49]. While some patient exhibit full

recovery after initiation of therapy, some patients can have persistent visual deficits [26, 48, 49, 51].

A variety of findings have been observed on ophthalmologic exam in patients with symptomatic ocular involvement attributed to aHUS. Greenwood et al. [49] described a 26-year-old female patient with presumed TTP receiving daily plasma exchange. The patient developed visual loss and was found to have hemorrhages of the optic disc, macula and retina. Areas of hemorrhage were identified in all four quadrants of the eyes bilaterally. Bilateral retinal artery and vein occlusions were present, along with vitreous hemorrhage. The patient demonstrated no improvement with plasma exchange and subsequent testing revealed an ADAMTS13 activity level of 61%. A diagnosis of aHUS was proposed, and the patient was started on eculizumab. Her renal function improved and she was able to discontinue hemodialysis. Follow-up ophthalmologic exam 7 months later showed clearing of her ocular occlusions and vitreous hemorrhage, with improvement in her visual acuity.

Pediatric case reports have described funduscopic examination findings including bilateral flame-shaped intraretinal hemorrhage, optic disc edema and tortuosity of the retinal vessels [48, 50]. Additional manifestations have included inferior rectus paralysis, choroidal hemorrhage, subhyaloid hemorrhage, premacular hemorrhage and retinal ischemia. Zheng et al. [48] described a case of recurrent ocular involvement in an 11-year-old female with aHUS with reduced visual acuity of 20/200 and 20/100 in the left and right eyes respectively. Ocular exam was notable for intraretinal hemorrhages, venous tortuosity and optic disc edema with central retinal vein occlusions and venous stasis retinopathy. After treatment with infusions of fresh frozen plasma and red blood cell, the patient's follow-up examination at 3-months revealed a normal funduscopic exam and 20/20 visual acuity bilaterally.

Given the potential severity of ocular manifestations in aHUS, prompt ophthalmologic exam should be performed in patients who exhibit ocular symptoms. Treatment with eculizumab can lead to rapid and significant improvement in ocular symptoms, even in cases of severe and prolonged visual deficits [51]. Continued treatment with eculizumab can lead to progressive resolution of ocular findings weeks to months after initiation of therapy [49].

Abdominal Visceral Manifestations of aHUS:

Gastrointestinal complications are common in aHUS, and certain factors, including the presence of Factor-H autoantibodies, may place children at increased risk for gastrointestinal involvement and complications [52]. While diarrhea is classically associated with the clinical prodrome of typical HUS, diarrhea is observed in approximately 50% [18–20] of patients preceding or during the acute phase of aHUS.

In a Turkish study by Besbas et al. [19], 10% of pediatric patients had gastrointestinal symptoms including vomiting, pancreatitis, cholelithiasis, transaminitis, hepatitis and gastrointestinal bleeding. In an international cohort of patients with aHUS, Johnson et al. [23] reported that the most common gastrointestinal symptoms were pancreatitis or pancreatic insufficiency and transaminitis, both occurring in approximately 8% of subjects.

Other symptoms included abdominal pain or feeding difficulties, intestinal perforation, cholestasis or cholelithiasis and gastrointestinal bleeding in 1 to 7% of patients. In individuals with anti-Factor H antibody associated disease, gastrointestinal symptoms can occur in greater than 80% of patients [18]. In a study of children with anti-Factor H antibody associated aHUS in the United Kingdom and Ireland, Brocklebank et al. [20] reported abdominal pain and vomiting in 56% of patients at the time of presentation. In the same cohort, 1 of 16 patients had pancreatitis and 2 of 16 patients had hepatitis.

Chronic gastrointestinal symptoms have also been described in patients with aHUS. Yao et al. [53] reported a 71-year-old female with history of persistent unexplained pancreatitis, who developed hemolytic anemia with schistocytes on peripheral smear and thrombocytopenia. Skin biopsy revealed endothelial deposition of C5b-9. Two weeks after initiation of eculizumab the patient had feeding difficulty, and was found to have pancreatic necrosis with ischemic colitis and perforation of the terminal ileum. Pathologic evaluation of the resected tissue demonstrated extensive C5b-9 deposition and microvascular thrombi. After completing four weeks of eculizumab treatment, the patient had normalization of her serum studies and resolution of her pancreatitis and other gastrointestinal manifestations. Another case report by Webb et al. [54] described a 16-year-old male with a 4-year history of treatment refractory ulcerative colitis, who developed acute kidney injury, hemolytic anemia and thrombocytopenia. Preceding admission to the hospital, the patient had two weeks of increased stool output and bloody stools. Stool studies were negative for *STEC*. Kidney biopsy revealed widespread TMA with positive staining for C5b-9 complement. The patient was started on eculizumab and had complete resolution of his gastrointestinal symptoms after seven weeks of therapy. The patient remains asymptomatic on chronic eculizumab treatment.

Other reported cases of aHUS in patients with inflammatory bowel disease (IBD) and treated with eculizumab have been described [55]. While a direct causal relationship cannot always be established, improvement in IBD symptoms has been demonstrated after treatment with complement blockade. Although such cases reports are infrequent, an evaluation for TMA should be considered in patients with treatment refractory abdominal diseases including IBD and pancreatitis.

Close monitoring for gastrointestinal symptoms should be performed, so that prompt evaluation and treatment of abdominal visceral complications can occur. Complications including pancreatic necrosis and ischemic colitis place patients at risk for increased morbidity and mortality. In some case, long-term gastrointestinal sequela of aHUS can result, including pancreatic insufficiency with insulin dependence [18].

Pulmonary Manifestations of aHUS:

Pulmonary complications of aHUS are typically seen in cases of multiple organ dysfunction and pulmonary edema associated with cardiac dysfunction and/or systemic volume overload [56]. Other reported pulmonary complications include pulmonary hemorrhage [57] and pulmonary embolism [40], which have been described in a few described cases of aHUS.

Dragon-Durey et al. [18] reported the death of one patient from pulmonary arterial hypertension before six months of age, who had anti-Factor H antibody associated disease.

A review by Johnson et al. [23] of 71 children with aHUS, revealed 15 (21%) patients developed respiratory failure requiring mechanical ventilation. While direct pulmonary injury is seen infrequently, respiratory failure secondary to pulmonary edema necessitating mechanical ventilation is a serious and life threating complication of aHUS. For this reason, careful monitoring of fluid and respiratory status is required to reduce the risk of pulmonary compromise in these patients.

Summary and Conclusions:

As reviewed, aHUS is a complex disease with a diverse range of clinical manifestations and complications. A high level of clinical suspicion is required to recognize irregular presentations of this already rare disease. Chronic cases of aHUS presenting as treatment refractory IBD and idiopathic pancreatitis have been discussed, and raise awareness of the potentially indolent course of some patients with aHUS. For this reason, evaluation of complement levels may be warranted at the initial diagnosis of these illnesses, to reduce the risk of morbidity and mortality associated with unopposed complement activation.

Confirmation of microangiopathic hemolysis by peripheral smear is key in identifying potential cases of aHUS, and differentiating it from other forms of Coombs-negative hemolytic anemia, including other rare disorders such a paroxysmal nocturnal hemoglobinuria (PNH) [58]. Testing of ADAMTS13 activity level and stool studies for STEC can further distinguish aHUS from other forms of TMA, including TTP and Shiga toxin positive HUS. If concern is present for SLE or other autoimmune or connective tissue disorders, screening for antiphospholipid antibodies including lupus anticoagulant and anticardiolipin antibodies should be considered. While serum studies are very helpful, a thorough clinical history is critical to evaluate for potential cases of medication induced TMA, which can help direct long treatment. Furthermore, genetic testing should be sent for all presumed cases of aHUS to guide clinical management and provide prognostic information on potential complications.

While the nomenclature of aHUS has evolved over time, ongoing research and genetic breakthroughs have shown that aHUS is a distinctly different clinical entity from Shiga toxin positive HUS. Although often clinically similar in their presentation, the pathogenesis and therefore the treatment of these two diseases differ vastly from one another. Recent identification of the *DGKE* gene mutation in some patients diagnosed with aHUS, also indicates that complement-independent forms of aHUS may exists. As our genetic and biological understanding of aHUS increases, we will likely require new nomenclature to define and categorize this complex umbrella of diseases.

Multiple Choice Questions (answers are provided following the reference list)

1. Mutations in this complement factor gene increase the risk of cardiovascular complications in aHUS to around 20%?

A. CFI

B. CFH

C. CFB

D. MCP

B - *CFH*

2. Diarrhea is a presenting symptom in approximately ___ % of patients with aHUS?

A. 10

B. 20

C. 40

D. 50

E. 80

D - 50%

3. Cardiovascular complications in aHUS are typically associated with atherosclerotic vascular disease?

A. True

B. False

B - False

4. Extra-renal manifestations of aHUS occur most often in this system, and are reported in 8 to 48% of cases.

A. Gastrointestinal

B. Ocular

C. Pulmonary

D. Cardiovascular

E. Neurologic

E - Neurologic

5. Abdominal visceral manifestations of aHUS include?

A. Pancreatitis

B. Ischemic colitis

C. Transaminitis

D. IBD

E. All of the above

E - All of the above

References

1. Ohanian M, Cable C, Halka K (2011) Eculizumab safely reverses neurologic impairment and eliminates need for dialysis in severe atypical hemolytic uremic syndrome. Clin Pharmacol 3:5–12. [PubMed: 22287852]
2. Talarico V, Aloe M, Monzani A, Miniero R, Bona G (2016) Hemolytic uremic syndrome in children. Minerva Pediatr 68:441–455. [PubMed: 27768015]
3. Taylor CM, Machin S, Wigmore SJ, Goodship TH, working party from the Renal Association tBCfSiH, the British Transplantation S (2010) Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol 148:37–47. [PubMed: 19821824]
4. Geerdink LM, Westra D, van Wijk JA, Dorresteijn EM, Lilien MR, Davin JC, Komhoff M, Van Hoeck K, van der Vlugt A, van den Heuvel LP, van de Kar NC (2012) Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics. Pediatr Nephrol 27:1283–1291. [PubMed: 22410797]
5. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, Daina E, Fenili C, Castelletti F, Sorosina A, Piras R, Donadelli R, Maranta R, van der Meer I, Conway EM, Zipfel PF, Goodship TH, Remuzzi G (2010) Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 5:1844–1859. [PubMed: 20595690]
6. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaime F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S, Niaudet P, Deschenes G, Lebranchu Y, Zuber J, Loirat C (2013) Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 8:554–562. [PubMed: 23307876]
7. Bu F, Maga T, Meyer NC, Wang K, Thomas CP, Nester CM, Smith RJ (2014) Comprehensive genetic analysis of complement and coagulation genes in atypical hemolytic uremic syndrome. J Am Soc Nephrol 25:55–64. [PubMed: 24029428]
8. Hindmarsh EJ, Marks RM (1998) Complement activation occurs on subendothelial extracellular matrix in vitro and is initiated by retraction or removal of overlying endothelial cells. J Immunol 160:6128–6136. [PubMed: 9637530]
9. Cataland SR, Wu HM (2014) How I treat: the clinical differentiation and initial treatment of adult patients with atypical hemolytic uremic syndrome. Blood 123:2478–2484. [PubMed: 24599547]
10. Manuelian T, Hellwage J, Meri S, Caprioli J, Noris M, Heinen S, Jozsi M, Neumann HP, Remuzzi G, Zipfel PF (2003) Mutations in factor H reduce binding affinity to C3b and heparin and surface attachment to endothelial cells in hemolytic uremic syndrome. J Clin Invest 111:1181–1190. [PubMed: 12697737]
11. Ritis K, Doumas M, Mastellos D, Micheli A, Giaglis S, Magotti P, Rafail S, Kartalis G, Sideras P, Lambris JD (2006) A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. J Immunol 177:4794–4802. [PubMed: 16982920]
12. Noris M, Mescia F, Remuzzi G (2012) STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol 8:622–633. [PubMed: 22986360]
13. Cofiell R, Kukreja A, Bedard K, Yan Y, Mickle AP, Ogawa M, Bedrosian CL, Faas SJ (2015) Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. Blood 125:3253–3262. [PubMed: 25833956]
14. Noris M, Remuzzi G (2009) Atypical hemolytic-uremic syndrome. N Engl J Med 361:1676–1687. [PubMed: 19846853]

15. Hofer J, Rosales A, Fischer C, Giner T (2014) Extra-renal manifestations of complement-mediated thrombotic microangiopathies. Front Pediatr 2:97. [PubMed: 25250305]
16. Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, Coppo R, Emma F, Johnson S, Karpman D, Landau D, Langman CB, Lapeyraque AL, Licht C, Nester C, Pecoraro C, Riedl M, van de Kar NC, Van de Walle J, Vivarelli M, Fremeaux-Bacchi V, International HUS (2016) An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol 31:15–39. [PubMed: 25859752]
17. Loirat C, Fremeaux-Bacchi V (2011) Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 6:60. [PubMed: 21902819]
18. Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, Andre JL, Takagi N, Cheong HI, Hari P, Le Quintrec M, Niaudet P, Loirat C, Fridman WH, Fremeaux-Bacchi V (2010) Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol 21:2180–2187. [PubMed: 21051740]
19. Besbas N, Gulhan B, Soylemezoglu O, Ozcakar ZB, Korkmaz E, Hayran M, Ozaltin F (2017) Turkish pediatric atypical hemolytic uremic syndrome registry: initial analysis of 146 patients. BMC Nephrol 18:6. [PubMed: 28056875]
20. Brocklebank V, Johnson S, Sheerin TP, Marks SD, Gilbert RD, Tyerman K, Kinoshita M, Awan A, Kaur A, Webb N, Hegde S, Finlay E, Fitzpatrick M, Walsh PR, Wong EKS, Booth C, Kerecuk L, Salama AD, Almond M, Inward C, Goodship TH, Sheerin NS, Marchbank KJ, Kavanagh D (2017) Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int 92:1261–1271. [PubMed: 28750931]
21. Shiari R, Parvaneh VJ, Dalirani R, Farivar S, Shiva MR (2014) Atypical hemolytic-uremic syndrome associated with antiphospholipid antibodies and antiphospholipid syndrome; a novel presentation. Pediatric Rheumatology 12:P363.
22. Neuhaus TJ, Calonder S, Leumann EP (1997) Heterogeneity of atypical haemolytic uraemic syndromes. Arch Dis Child 76:518–521. [PubMed: 9245850]
23. Johnson S, Stojanovic J, Ariceta G, Bitzan M, Besbas N, Frieling M, Karpman D, Landau D, Langman C, Licht C, Pecoraro C, Riedl M, Siomou E, van de Kar N, Walle JV, Loirat C, Taylor CM (2014) An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome. Pediatr Nephrol 29:1967–1978. [PubMed: 24817340]
24. Fidan K, Goknar N, Gulhan B, Melek E, Yildirim ZY, Baskin E, Hayran M, Gulleroglu K, Ozcakar ZB, Ozaltin F, Soylemezoglu O (2018) Extra-Renal manifestations of atypical hemolytic uremic syndrome in children. Pediatr Nephrol 33:1395–1403. [PubMed: 29610995]
25. Diamante Chiodini B, Davin JC, Corazza F, Khaldi K, Dahan K, Ismaili K, Adams B (2014) Eculizumab in anti-factor h antibodies associated with atypical hemolytic uremic syndrome. Pediatrics 133:e1764–1768. [PubMed: 24843055]
26. Gulleroglu K, Fidan K, Hancer VS, Bayrakci U, Baskin E, Soylemezoglu O (2013) Neurologic involvement in atypical hemolytic uremic syndrome and successful treatment with eculizumab. Pediatr Nephrol 28:827–830. [PubMed: 23389237]
27. Salem G, Flynn JM, Cataland SR (2013) Profound neurological injury in a patient with atypical hemolytic uremic syndrome. Ann Hematol 92:557–558. [PubMed: 23139014]
28. Koehl B, Boyer O, Biebuyck-Gouge N, Kossorotoff M, Fremeaux-Bacchi V, Boddaert N, Niaudet P (2010) Neurological involvement in a child with atypical hemolytic uremic syndrome. Pediatr Nephrol 25:2539–2542. [PubMed: 20714753]
29. Tsai HM, Kuo E (2014) Eculizumab therapy leads to rapid resolution of thrombocytopenia in atypical hemolytic uremic syndrome. Adv Hematol 2014:295323. [PubMed: 25400666]
30. Noris M, Remuzzi G (2014) Cardiovascular complications in atypical haemolytic uraemic syndrome. Nat Rev Nephrol 10:174–180. [PubMed: 24419569]
31. Vilalta R, Lara E, Madrid A, Chocron S, Munoz M, Casquero A, Nieto J (2012) Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome. Pediatr Nephrol 27:2323–2326. [PubMed: 22890512]

32. Sallee M, Daniel L, Piercecchi MD, Jaubert D, Fremeaux-Bacchi V, Berland Y, Burtey S (2010) Myocardial infarction is a complication of factor H-associated atypical HUS. Nephrol Dial Transplant 25:2028–2032. [PubMed: 20305136]
33. Hu H, Nagra A, Haq MR, Gilbert RD (2014) Eculizumab in atypical haemolytic uraemic syndrome with severe cardiac and neurological involvement. Pediatr Nephrol 29:1103–1106. [PubMed: 24317637]
34. Loirat C, Macher MA, Elmaleh-Berges M, Kwon T, Deschenes G, Goodship TH, Majoie C, Davin JC, Blanc R, Savatovsky J, Moret J, Fremeaux-Bacchi V (2010) Non-atheromatous arterial stenoses in atypical haemolytic uraemic syndrome associated with complement dysregulation. Nephrol Dial Transplant 25:3421–3425. [PubMed: 20530807]
35. Davin JC, Gracchi V, Bouts A, Groothoff J, Strain L, Goodship T (2010) Maintenance of kidney function following treatment with eculizumab and discontinuation of plasma exchange after a third kidney transplant for atypical hemolytic uremic syndrome associated with a CFH mutation. Am J Kidney Dis 55:708–711. [PubMed: 19854549]
36. Vergouwen MD, Adriani KS, Roos YB, Groothoff JW, Majoie CB (2008) Proximal cerebral artery stenosis in a patient with hemolytic uremic syndrome. AJNR Am J Neuroradiol 29:e34. [PubMed: 18258702]
37. Davin JC, Majoie C, Groothoff J, Gracchi V, Bouts A, Goodship TH, Loirat C (2011) Prevention of large-vessel stenoses in atypical hemolytic uremic syndrome associated with complement dysregulation. Pediatr Nephrol 26:155–157. [PubMed: 20652819]
38. Bekassy ZD, Kristoffersson AC, Cronqvist M, Roumenina LT, Rybkine T, Vergoz L, Hue C, Fremeaux-Bacchi V, Karpman D (2013) Eculizumab in an anephric patient with atypical haemolytic uraemic syndrome and advanced vascular lesions. Nephrol Dial Transplant 28:2899–2907. [PubMed: 24009284]
39. Bhatti NK, Karimi Galougahi K, Paz Y, Nazif T, Moses JW, Leon MB, Stone GW, Kirtane AJ, Karmpaliotis D, Bokhari S, Hardy MA, Dube G, Mohan S, Ratner LE, Cohen DJ, Ali ZA (2016) Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease. J Am Heart Assoc doi: 10.1161/JAHA.116.003648.
40. Mallett A, Hughes P, Szer J, Tuckfield A, Van Eps C, Cambell SB, Hawley C, Burke J, Kausman J, Hewitt I, Parnham A, Ford S, Isbel N (2015) Atypical haemolytic uraemic syndrome treated with the complement inhibitor eculizumab: the experience of the Australian compassionate access cohort. Intern Med J 45:1054–1065. [PubMed: 26247170]
41. Le Quintrec M, Zuber J, Moulin B, Kamar N, Jablonski M, Lionet A, Chatelet V, Mousson C, Mourad G, Bridoux F, Cassuto E, Loirat C, Rondeau E, Delahousse M, Fremeaux-Bacchi V (2013) Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. Am J Transplant 13:663–675. [PubMed: 23356914]
42. Roumenina LT, Frimat M, Miller EC, Provot F, Dragon-Durey MA, Bordereau P, Bigot S, Hue C, Satchell SC, Mathieson PW, Mousson C, Noel C, Sautes-Fridman C, Halbwachs-Mecarelli L, Atkinson JP, Lionet A, Fremeaux-Bacchi V (2012) A prevalent C3 mutation in aHUS patients causes a direct C3 convertase gain of function. Blood 119:4182–4191. [PubMed: 22246034]
43. Ozel A, Caliskan U, Gucer S (2003) Peripheral gangrene complicating hemolytic uremic syndrome in a child. Pediatr Nephrol 18:465–467. [PubMed: 12736810]
44. Ardissino G, Tel F, Testa S, Marzano AV, Lazzari R, Salardi S, Edefonti A (2014) Skin involvement in atypical hemolytic uremic syndrome. Am J Kidney Dis 63:652–655. [PubMed: 24290245]
45. Kaplan BS, Garcia CD, Chesney RW, Segar WE, Giugno K, Chem R (2000) Peripheral gangrene complicating idiopathic and recessive hemolytic uremic syndromes. Pediatr Nephrol 14:985–989. [PubMed: 10975312]
46. Malina M, Gulati A, Bagga A, Majid MA, Simkova E, Schaefer F (2013) Peripheral gangrene in children with atypical hemolytic uremic syndrome. Pediatrics 131:e331–335. [PubMed: 23230076]
47. Sturm V, Menke MN, Landau K, Laube GF, Neuhaus TJ (2010) Ocular involvement in paediatric haemolytic uraemic syndrome. Acta Ophthalmol 88:804–807. [PubMed: 19604154]

48. Zheng X, Gorovoy IR, Mao J, Jin J, Chen X, Cui QN (2014) Recurrent ocular involvement in pediatric atypical hemolytic uremic syndrome. J Pediatr Ophthalmol Strabismus 51:e62–65.

49. Greenwood GT (2015) Case report of atypical hemolytic uremic syndrome with retinal arterial and venous occlusion treated with eculizumab. Int Med Case Rep J 8:235–239. [PubMed: 26508891]

50. Larakeb A, Leroy S, Fremeaux-Bacchi V, Montchilova M, Pelosse B, Dunand O, Deschenes G, Bensman A, Ulinski T (2007) Ocular involvement in hemolytic uremic syndrome due to factor H deficiency--are there therapeutic consequences? Pediatr Nephrol 22:1967–1970. [PubMed: 17619907]

51. Ramos de Carvalho JE, Schlingemann RO, Oranje M, Bemelman FJ, van Schooneveld MJ (2017) Reversal of threatening blindness after initiation of eculizumab in Purtscher-like retinopathy secondary to atypical hemolytic uremic syndrome. Int Ophthalmol 38:399–407. [PubMed: 28275964]

52. Berger BE (2016) The Alternative Pathway of Complement and the Evolving Clinical-Pathophysiological Spectrum of Atypical Hemolytic Uremic Syndrome. Am J Med Sci 352:177–190. [PubMed: 27524217]

53. De Yao J, Kaplan R, Magro C (2015) An Atypical Case of Atypical Hemolytic Uremic Syndrome: Predominant Gastrointestinal Involvement, Intact Renal Function, and C5b-9 Deposition in Colon and Skin. J Hematol 4:193–195

54. Webb TN, Griffiths H, Miyashita Y, Bhatt R, Jaffe R, Moritz M, Hofer J, Swiatecka-Urban A (2015) Atypical Hemolytic Uremic Syndrome and Chronic Ulcerative Colitis Treated with Eculizumab. Int J Med Pharm Case Reports 4:105–112. [PubMed: 27135055]

55. Green H, Harari E, Davidovits M, Blickstein D, Grossman A, Gafter U, GafterGvili A (2014) Atypical HUS due to factor H antibodies in an adult patient successfully treated with eculizumab. Ren Fail 36:1119–1121. [PubMed: 24828571]

56. Roman-Ortiz E, Mendizabal Oteiza S, Pinto S, Lopez-Trascasa M, Sanchez-Corral P, Rodriguez de Cordoba S (2014) Eculizumab long-term therapy for pediatric renal transplant in aHUS with CFH/CFHR1 hybrid gene. Pediatr Nephrol 29:149–153. [PubMed: 23982707]

57. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C, French Society of Pediatric N (2007) Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 18:2392–2400. [PubMed: 17599974]

58. Borowitz MJ, Craig FE, Digiuseppe JA, Illingworth AJ, Rosse W, Sutherland DR, Wittwer CT, Richards SJ, Clinical Cytometry S (2010) Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry B Clin Cytom 78:211–230. [PubMed: 20533382]

Summary Points:

- aHUS is a rare and complicated disease with many different clinical presentations.
- Neurological symptoms are the most common extra-renal manifestation of aHUS and can occur in 8 to 48% of cases.
- Altered mental status and seizures can results from a variety of causes during the acute and chronic phase of aHUS including hypertension, ischemia, uremia, electrolyte derangements and cerebral edema.
- Diarrhea is a common prodromal symptom in patients with aHUS.
- Treatment refractory IBD and idiopathic pancreatitis can be a presenting symptom of aHUS
- *CFH* gene mutations and anti-Factor H antibodies have been associated with an increased incidence of extra-renal gastrointestinal and cardiovascular manifestations in patients with aHUS.
- STEC testing, ADAMTS13 activity level, peripheral blood smear and genetic testing should be obtained to differentiate aHUS from other forms of hemolytic anemia and TMA including Shiga toxin positive HUS, TTP, and paroxysmal nocturnal hemoglobinuria.

Table 1.

Overview of case reports describing skin and peripheral vascular manifestations

			Presenting Features									
Case	**Age**	**Gender**	**Presenting Symptoms**	**Initial Therapy**	**Laboratory Test Results**					**Skin/ Peripheral Vascular Manifestations**	**Molecular Defects**	**Reference**
					HgB (g/dl)	**Platelets (/mm^3)**	**LDH (U/l)**	**Serum Creatinine (mg/dl)**	**C3**			
1	3 yr	Male	Malaise, pallor and cutaneous rash.	FFP infusions and PD.	3.3	84,000	9,980	4	31 mg/dl (normal 90180 mg/dl)	Diffuse petechiae and nailbed discoloration that progressed to ischemic changes of the upper and lower extremity digits and gangrene. Cutaneous symptoms did not improve with dextran infusions, nitroglycerin or local captopril application. Improved perfusion proximal to areas of necrosis occurred following treatment with plasma pheresis and FFP infusions.	N/A[a]	[43]
2	4 yr	Female	Pallor, oliguria and edema.	Plasmapheresis with FFP.	7.2	42,000	6,000	7.5	0.32 mg/ml (normal 0.89 – 1.78 mg/ml)	Poor perfusion and cyanosis of the left upper extremity digits progressing to gangrene despite treatment with oral pentoxifylline. Patient was started on home PD and died three weeks later from complications.	CFHR1-R3 deletion and presence of anti-Factor Hantibodies	[46]
3	9 mo	Female	Presented at 4 months of age with hypertension and edema.	PD and plasma infusions.	N/A	135	400	N/A	0.5 mg/ml (normal > 0.6 mg/ml)	Discoloration of the right and left upper and lower extremity digits occurred following discontinuation of plasma infusions. Right upper extremity changes progressed to painful	Heterozygous mutation of the *C3* gene causing loss of C3 convertase regulation by factor H	[46]

			Presenting Features									
Case	**Age**	**Gender**	**Presenting Symptoms**	**Initial Therapy**	**Laboratory Test Results**					**Skin/ Peripheral Vascular Manifestations**	**Molecular Defects**	**Reference**
					HgB (g/dl)	**Platelets (/mm^3)**	**LDH (U/l)**	**Serum Creatinine (mg/dl)**	**C3**			
										ischemia and gangrene of digits II-V that was unresponsive to plasma exchange and continuous prostacyclin infusion. The patient's ischemic pain resolved rapidly following initiation of eculizumab, with improved perfusion proximal to areas of existing gangrene.		
4	7 yr	Male	Vomiting, diarrhea, generalized edema, and abdominal pain.	CVVHD and plasmapheresis with FFP replacement, followed by transition to HD	6.1	110,000	N/A	3.7	46 mg/dl (normal 87181 mg/dl)	Purpuric rash on the dorsal aspect of the feet, which progressed to a confluent ecchymotic, nonblanching rash over feet bilaterally with cool lower extremity digits. Subsequent developed on purple, nonblanching maculates and papules over arms, trunk and back. Necrotic autoamputation of lower extremity digits occurred.	N/A[a]	[45]
5	19 mo	Female	Flu-like illness, lower extremity hematomas, and decreased peripheral perfusion.	Exchange transfusions, FFP, PD, IV nitroglycerin and sympathetic blockage.	11.2	20,000	9,031	3.09	N/A	Poor peripheral perfusion with cyanosis of the upper and lower extremity digits, with rapid progression to gangrene.	N/A[a]	[45]
6	2 yr	Female	Pallor, oliguria and edema.	N/A	6.7	51,000	1,950	6.7	N/A	Discoloration of the upper and lower extremity digits with progression to necrosis, with subsequent autoamputation	N/A[a]	[45]

			Presenting Features									
Case	**Age**	**Gender**	**Presenting Symptoms**	**Initial Therapy**	**Laboratory Test Results**					**Skin/ Peripheral Vascular Manifestations**	**Molecular Defects**	**Reference**
					HgB (g/dl)	**Platelets (/mm^3)**	**LDH (U/l)**	**Serum Creatinine (mg/dl)**	**C3**			
										of multiple digits.		
7	32 yr	Female	ESRD	HD	N/A	265	378	N/A	N/A	Severe pain in the bilateral perimalleolar areas with subsequent development of superficial ulcerations. Symptoms and skin changes resolved following initiation of PE three days per week.	CFH gene mutation	[44]
8	21 yr	Male	Severe headache, nephrotic range proteinuria, and ESRD at the age of 19	HD	N/A	105	295	N/A	0.66 mg/ml (normal range NA)	Numerous lower extremity violaceous maculopapular and ulcerative-necrotic lesions and petechiae, which resolved following treatment with tandem PE-HD followed by eculizumab.	Anti-factor H antibodies	[44]
9	19 yr	Male	aHUS onset at 6 months of age with developm ent of ESRD	Dialysis, followed by successful renal transplant at age 17. Patient receiving regular plasma infusions	N/A	318	313	2.49	N/A	Lower extremity purpuric and ulcerative-necrotic skin lesions, which resolved following treatment with eculizumab.	CFH gene mutation	[44]

[a]Some of the cases presented in this table occurred prior to standardized testing for molecular defects, and therefore were classified as idiopathic, recessive or diarrhea-negative hemolytic uremic syndrome (HUS). *CFH* complement factor H, *CVVHD* continuous venovenous hemodiafiltration, *ESRD* end stage renal disease, *FFP* fresh frozen plasma, *HD* hemodialysis, *mo* months, *N/A* not available, *PD* peritoneal dialysis, *PE* plasma exchange, *yr* years