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ORIGINAL PAPER

A time for reappraisal of "atypical" hemolytic uremic syndrome: should all patients be treated the same?

Rebecca L. Ruebner · Bernard S. Kaplan · Lawrence Copelovitch

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Abstract Atypical hemolytic uremic syndrome (HUS) refers to the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury in the absence of Shiga toxin-producing *Escherichia coli* exposure or *Streptococcus pneumoniae* infection. Currently, approximately 50 % of the atypical cases have demonstrable mutations in complement regulatory proteins. Historically, the diagnosis of atypical HUS portends a poor prognosis with a high rate of disease recurrence, progression to end-stage renal disease, and death. However, it is now evident that atypical HUS actually encompasses a heterogeneous group of disorders, and there are reports suggesting that some cases of atypical HUS have a favorable prognosis, similar to that of diarrhea-associated disease. We present three patients with the atypical HUS phenotype who had complete renal recovery and no disease recurrence. We believe it is important to distinguish those cases of atypical HUS associated with disorders of complement regulatory proteins from other idiopathic causes of nondiarrheal HUS given the implications for prognosis and treatment. *Conclusion*: Given the heterogeneous nature and variable prognosis of atypical HUS, treatment should be carefully considered prior to the use of long-term plasma therapy and/or eculizumab.

Keywords Atypical hemolytic uremic syndrome · Thrombotic microangiopathy · Eculizumab · Nondiarrheal HUS · Microangiopathic hemolytic anemia · Complement proteins · Acute kidney injury

R. L. Ruebner · B. S. Kaplan · L. Copelovitch (✉)
Division of Nephrology, Department of Pediatrics, The Children's Hospital of Philadelphia,
1 Main, 34th Street and Civic Center Boulevard,
Philadelphia, PA 19104, USA
e-mail: copelovitch@email.chop.edu

Introduction

It has long been recognized that there are many subtypes and variants of the hemolytic uremic syndrome (HUS) [15]. HUS is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI). Approximately 90 % of cases of HUS in children occur after a diarrheal illness with Shiga-like toxin-producing bacteria, usually strains of enterohemorrhagic *Escherichia coli* and, less frequently, *Shigella dysenteriae* [4, 16]. Shiga toxin-producing *E. coli* (STEC) HUS (diarrheal or typical) usually occurs in children aged 6 months to 5 years and carries a favorable prognosis, with 75 % of patients achieving full long-term recovery [11]. HUS can also occur with *Streptococcus pneumoniae* infection [5, 7].

The remaining 10 % of cases of HUS in children have been grouped into a category referred to as "atypical" HUS. The term atypical was first introduced by Barnard and Kibel in 1965 to differentiate nine patients with diarrhea-associated HUS from two others without a diarrheal prodrome [2]. The term was subsequently used by Fitzpatrick et al. to differentiate typical, diarrhea-associated cases of HUS from nondiarrheal atypical cases [10]. Atypical cases present at any time of year, and many have a family history of HUS with similar age of onset [14]. They often have an insidious presentation, severe arterial hypertension, a relapsing course, and inexorable progression [13].

Although the term atypical HUS was historically used to designate cases of HUS not associated with diarrhea or *S. pneumoniae* infection, it is now evident that this category actually encompasses a very heterogeneous group of disorders. With the advent of molecular and genetic diagnostics, it is now known that at least 50 % of cases of atypical HUS are caused by inherited mutations in complement regulation [6]. Mutations have been identified in complement factor H

(CFH), complement factor I (CFI), membrane cofactor protein (MCP or CD46), complement factor B (CFB), C3 convertase components (C3), and thrombomodulin (THBD) [22], and it is likely that additional mutations will continue to be discovered. Atypical HUS can also result from autoantibodies directed at factor H with resultant functional deficiency [9, 20] and possibly mutations in clusterin [29]. Other disorders grouped under the rubric of atypical HUS include defects in cobalamin metabolism. Secondary causes of HUS are human immunodeficiency virus (HIV), malignancy, calcineurin inhibitors, transplantation, and rheumatologic diseases [3]. A proposed classification is presented in Table 1.

Historically, patients with atypical HUS had a poor prognosis and a high risk of disease recurrence, progression to end-stage renal disease (ESRD), and death [22, 27]. However, there are reports that some patients with atypical HUS have a favorable prognosis similar to diarrhea-associated disease [17, 21, 24, 28]. We describe three patients who presented with the features of nondiarrheal HUS but had no evidence for an underlying disorder of complement regulation on genetic and molecular testing. All three patients had renal biopsies; two had no evidence of thrombotic microangiopathy and one had cortical necrosis which was impossible to distinguish from isolated HUS. All three patients recovered completely, and none has had recurrence of disease thus far.

We report these patients to illustrate the phenotypic diversity of atypical HUS. In the current era of molecular and genetic diagnostic testing, it is important to separate those patients with inherited complement regulatory proteins from other idiopathic causes of nondiarrheal HUS given the implications for prognosis and treatment. With the introduction of an important new therapy, eculizumab, we believe that it is essential to define cases better prior to subjecting all atypical patients to this treatment.

Table 1 Classification

Hemolytic Uremic Syndrome
Acquired
STEC, *S. dysenteriae*
S. pneumoniae
Anti-CFH antibodies
Other clinical associations
HIV
Malignancy
Transplantation
Medications (i.e., calcineurin inhibitors, mitomycin C, gemcitabine, VEGF inhibitors, oral contraceptives)
Rheumatologic (i.e., antiphospholipid antibody syndrome)
Acute postinfectious glomerulonephritis
Inherited
Mutations in complement regulatory proteins
Defective cobalamin metabolism
Idiopathic
Thrombotic Thrombocytopenic Purpura
Acquired
Anti-ADAMTS13 antibodies
Medications (i.e., quinine, ticlopidine, clopidogrel)
Rheumatologic (i.e., systemic lupus erythematosus)
Inherited
Mutations in ADAMTS13 (Upshaw–Schulman syndrome)

Patient presentations

Patient 1

A 15-month-old healthy White female presented with seizures after several days of fever, cough, and upper respiratory symptoms. There was no history of diarrhea. Blood pressure was 90/45 mmHg. Physical examination was notable for pallor, and the liver was palpable 3 cm below the costal margin. Neurologic examination was normal. Laboratory values were consistent with HUS and are presented in Table 2. Additional pertinent laboratory studies were consistent with liver injury: alanine aminotransferase, 9,743 U/L (normal, 5–45 U/L); aspartate aminotransferase, 11,371 U/L (normal, 20–60 U/L); serum albumin concentration, 2.6 g/dl (normal, 3.5–4.6 g/dl); prothrombin time, 21.6 s (normal, 11–13.5 s); international normalized ratio test, 2.07; and partial thromboplastin, 40 s (normal, 21–35 s). Serum complement C3 concentration was transiently low at 18 mg/dl (normal, 78–169 mg/dl) and serum C4 concentration at 1.8 mg/dl (normal, 16–45 mg/dl) in the setting of acute liver failure; however, repeat levels 2 weeks later had normalized (C3, 106 mg/dl; C4, 16.3 mg/dl) and remained normal 2 months later (C3, 99 mg/dl; C4, 26 mg/dl). A brain magnetic resonance imaging (MRI) showed cerebellitis considered to be of viral etiology.

Course

Over the next week, she became hypertensive and oliguric with progressive rise in serum creatinine concentration from 1.4 to 2.9 mg/dl. A renal biopsy showed no evidence of thrombotic microangiopathy (details in Table 3). Due to ongoing oliguria, volume overload, and hypertension, she required continuous venovenous hemodiafiltration (CVVHDF) for 7 days. She was treated with plasmapheresis with plasma infusions for 4 weeks based on the European Study Group guideline [1]. Plasmapheresis was discontinued after 4 weeks, and she had complete recovery of liver function and normalization of serum creatinine and hematologic parameters. After

Table 2 Laboratory results of three cases of HUS

Patient	Age	Sex	Peak serum creatinine (mg/dl)	Lowest hemoglobin (normal, 10.5–13.5 g/dl)	Lowest platelet count (normal, 150,000–400,000/μl)	LDH (normal, 500–920 U/L)	Coombs test	Schistocytes	Proteinuria	ADAMTS13	Initial C3 (normal, 78–169 mg/dl)	Infectious testing
1	15 months	F	2.9	6.4	43,000	25,000	Negative	Present	3+; protein to creatinine ratio, 3.7 mg/mg	Normal, no inhibitor	18	Negative stool culture; normal chest radiograph; negative blood culture; +RSV; +human metapneumovirus
2	17 years	F	3.0	7.8	32,000	3181	Negative	Present	2+	Normal, no inhibitor	85	Negative stool culture; normal chest radiograph; negative blood culture; negative viral studies
3	23 months	M	5.5	5.5	33,000	14,069	Negative	Present	2+	Normal, no inhibitor	108	Negative stool culture; normal chest radiograph; negative blood culture; +rhinovirus from nasal aspirate; +HHV-6 PCR from blood

2 years, she has had no recurrences, has normal blood pressure, no proteinuria, and normal serum creatinine.

Patient 2

A 17-year-old healthy White female presented with progressive lower extremity weakness leading to paralysis and respiratory failure. A spinal MRI demonstrated transverse myelitis. She was treated with intravenous methylprednisolone, intravenous immunoglobulin, plasmapheresis, and one dose of intravenous cyclophosphamide for the transverse myelitis. One month after admission to the hospital, she developed oliguric AKI, anemia with schistocytes, and thrombocytopenia. There was no preceding diarrhea. Blood pressure was 107/56 mmHg. Physical examination was normal except for the neurologic examination which was notable for diminished strength, sensation, and areflexia in the lower extremities. Laboratory values are presented in Table 2. Additional laboratory studies included negative antinuclear, DNA binding, antineutrophil cytoplasmic, anti-β2-glycoprotein, and anticardiolipin antibodies.

Course

She became hypertensive and oliguric with a progressive decline in renal function, and she required CVVHDF for 3 days. A renal biopsy showed acute tubular necrosis but no evidence of thrombotic microangiopathy (Table 3). Initially, she underwent plasmapheresis with plasma infusions for 3 weeks for the treatment of transverse myelitis. The HUS phenotype developed while she was receiving plasmapheresis; treatment was continued for an additional 3 days. Improving urine output and renal function led to discontinuation of plasmapheresis. She had normalization of serum creatinine and hematologic values and steady improvement in neurologic symptoms with improving strength and sensation in her lower extremities. She was discharged to a rehabilitation facility to complete her recovery and has not had any recurrences at 22-month follow-up.

Patient 3

A 23-month-old healthy White male presented with several days of fever, emesis, and oliguria. There was no diarrhea. Blood pressure was 93/63 mmHg. Physical examination was normal. Laboratory values were consistent with HUS and are presented in Table 2.

Course

Over the following 2 days, the serum creatinine concentration increased from 3.1 mg/dl on presentation to a peak of 5.5 mg/dl. A renal biopsy showed cortical necrosis which

Table 3 Additional results and clinical course of three cases of HUS

Patient	CFH and CFI (normal CFH, 160–412 mcg/ml; normal CFI, 29–58.5 mcg/ml)	Genetic mutations	Renal biopsy	Plasma therapy	Dialysis
1	CFH, 202	CFH, normal; CFI, normal; MCP, normal; CFHR5, normal	Light microscopy: 15 normal-sized, normal-appearing glomeruli. Tubules were normal; a few contained cellular casts compatible with shed tubular epithelium. No interstitial infiltrate. The extraglomerular blood vessels were thick-walled, suggestive of hypertensive change. No microthrombi were seen. Immunofluorescence: negative for IgA, IgG, IgM, C3, and C1q. Electron microscopy: foot processes were focally effaced or clumped. No electron dense deposits were seen.	Plasmapheresis, ×4 weeks	CVVHDF, ×7 days
2	CFH, 154; CFI, 33.5	CFH, normal; CFI, normal; MCP, normal; CFHR5, normal; C3, normal; CFB, normal; THBD, normal	Light microscopy: eight normal-sized, normal-appearing glomeruli. Tubules showed marked reactive changes with necrotic tubular cells, mitotic figures, nuclear pleomorphism, and granular, eosinophilic necrotic cell debris. The interstitium was normal. Arterioles were normal with no necrosis or thrombosis. Immunofluorescence: negative for IgA, IgG, and C1q. IgM and C3 were weakly positive. Electron microscopy: no immune complex deposits were noted. Foot processes were well individualized. No capillary thrombi were noted. Tubular epithelium exhibited degenerative changes.	Plasmapheresis, ×3 weeks	CVVHDF, ×3 days
3	CFH, 363; CFI, 58.6	CFH, normal; CFI, normal; MCP, normal; CFHR5, normal; C3, normal; CFB, normal; THBD, normal	Light microscopy: 26 glomeruli were seen. There was moderate to severe necrosis predominantly involving the tubules and extending to the glomeruli accompanied by interstitial edema and a mild inflammatory infiltrate. There were several foci of fibrin deposition within capillary lumens, many of which appeared centered at the vascular pole. Larger arteries were uninvolved. Immunofluorescence: IgG stained no glomeruli. IgA and C3 stained 2/2 glomeruli partially as peripheral extracapillary granules. IgM stained 2/2 glomeruli as fine granules in the mesangium and coarse globules in capillaries. Fibrinogen stained 2/2 glomeruli in a global pattern with capillary lumen accentuation. Electron microscopy: images of a single glomerulus showed prominent endothelial cells and wrinkling of the basement membrane accompanied by an increase in mesangial matrix. No deposits were seen within the glomerular basement membrane.	Plasma infusions, ×6 days	Peritoneal dialysis, ×14 days

was impossible to distinguish from isolated HUS (Table 3). He required peritoneal dialysis for 14 days for fluid balance. He was treated with plasma infusions daily for 6 days and serum creatinine and hematological values normalized. At 16-month follow-up, he has had no recurrences and has normal blood pressure and serum creatinine.

Discussion

Currently, the term atypical HUS is used to designate cases of HUS not associated with diarrhea or *S. pneumoniae* infection, and about 50 % is caused by mutations in complement regulatory proteins [6]. In a French cohort of 46

children with atypical HUS, 22 % had CFH mutation, 13 % had CFI mutation, 15 % had MCP mutation, and in 48 %, no genetic mutation could be identified. Onset of disease was before 2 years of age in 70 % of patients [27]. In another cohort of 167 children with nondiarrheal HUS, 34 (20 %) had identified mutations in complement regulators: 65 % of these had CFH mutations, 18 % had CFI mutations, and 18 % had MCP mutations. An additional 22 patients had suspected disorders of complement regulation because of low C3 levels and relapsing disease, and another eight cases were familial among four sibling pairs. Of note, 90 patients could not be further characterized [3].

Atypical HUS has been reported to have a poor prognosis with a high risk of disease recurrence and higher rates of ESRD and mortality compared to typical HUS, particularly in patients with CFH or CFI mutations [18, 27, 30]. In the French cohort, 54 % of patients had between two and nine relapses of HUS 1 month to 9 years after presentation. Among patients with CFH mutation, 80 % died or reached ESRD at the first episode or after relapses compared to 50 % of patients with CFI mutation, 29 % with MCP mutation, and 32 % with no identified mutation. Among all cases, 37 % of patients died or developed ESRD within 1 year of presentation. At 5-year follow-up, rates of ESRD were 73, 50, 38, and 32 % in CFH, CFI, MCP, and no identified mutation groups, respectively. A total of 24 kidney transplants were performed in 15 patients; six had recurrence of HUS and 66 % had at least one graft failure [27].

However, other studies have suggested that not all patients with so-called atypical HUS have an unfavorable prognosis. Kelles et al. reported a cohort of 95 patients with HUS, of whom 12 had atypical disease; there was no difference in mortality or ESRD between the two groups [17]. Proesmans reported 20 patients with nondiarrheal HUS from 1969 to 1993, 14 of whom recovered completely with normal renal function at long-term follow-up. There were no differences in hematologic features between those who recovered fully and those with unfavorable outcome. The group that had an unfavorable prognosis had more severe renal disease during the initial presentation, with a greater incidence of hypertension, oligoanuria, and need for acute dialysis. Proesmans concluded that there is a mild variant of atypical HUS with an excellent prognosis in the absence of any therapy [24]. Siegler et al. compared 28 episodes of atypical HUS with 266 cases of diarrhea-associated HUS from 1970 to 1993. Patients with atypical HUS tended to be older than patients with diarrhea-associated disease. There were no differences in hematocrit or platelet counts on presentation between the two groups. Serum creatinine concentrations and blood urea nitrogen were lower in the patients with atypical disease at presentation, oligoanuria was less frequent, and they were less likely to require dialysis compared to the patients with diarrhea-associated HUS. Patients with atypical HUS were less likely to have seizures. A minority (18 %) of the patients with atypical HUS had recurrent disease, and there were no deaths in the atypical group compared to 3.4 % of patients who died in the typical group. At their last follow-up, the prevalence of hypertension, proteinuria, and estimated glomerular filtration rate <90 ml/min/1.73 m^2 was similar between both groups, and there was no significant difference in the incidence of ESRD between those with typical and atypical disease [28].

The current treatment of atypical HUS includes plasma therapy and plasmapheresis with plasma replacement [1, 19, 25, 26]. A guideline for the management of atypical HUS was proposed by the European Study Group for HUS. Patients who meet the clinical criteria for HUS with no history of diarrhea, no evidence of invasive *S. pneumoniae* infection, age <6 months, relapse of HUS, or family history of HUS should undergo investigation for disorders of complement regulation. Plasmapheresis should be initiated empirically within 24 h of diagnosis of suspected atypical HUS. It was suggested that given that at least 50 % of atypical patients have some form of complement dysregulation, plasmapheresis should be initiated empirically while waiting for the confirmatory laboratory tests, which may take time to complete. Plasmapheresis is recommended daily for 5 days, then five sessions per week for 2 weeks, then three sessions per week for 2 weeks. Exceptions to initiating plasmapheresis include suspected inherited ADAMTS13 deficiency in which case plasma infusions would be recommended, strong clinical suspicion for cobalamin C deficiency, or the clinician's belief that the risks of plasmapheresis outweigh the benefit to a patient with only mild renal involvement [1].

More recently, eculizumab, a humanized monoclonal antibody against terminal complement protein C5, has been used to treat patients with confirmed or suspected mutations in complement regulators and to prevent posttransplant recurrence of HUS [8, 12, 23, 31, 32]. Initial case reports and Alexion™-sponsored phase II trials suggest effective results in patients with plasmapheresis-resistant atypical HUS and those being treated with chronic plasma therapy. The main side effects of eculizumab include potentially life-threatening infection with *Neisseria meningitides* and infusion reactions. Although eculizumab has been used for many years for the treatment of paroxysmal nocturnal hemoglobinuria, the full therapeutic benefit and potential harms have not been fully elucidated for atypical HUS. Eculizumab is also an extremely expensive therapy, with costs up to $400,000 per year of treatment.

Eculizumab is a very promising therapy for those patients with inherited mutations in complement leading to HUS. However, the three patients in this report contribute to the body of literature that suggests that the current designation of atypical HUS actually embodies a heterogeneous group

of disorders and that some patients may have a favorable prognosis with the potential for full recovery. We believe this is why it is critical to differentiate those patients with suspected or confirmed mutations in complement regulatory proteins from other idiopathic cases of atypical HUS in order to guide therapy.

We would be hesitant to commit all patients with an atypical HUS phenotype to long-term therapy with eculizumab. Rather, at this time, we would suggest that a stepwise approach be used in the management of atypical HUS in order to prevent all patients from being committed to chronic plasma therapy or eculizumab. Given the high morbidity and mortality associated with inherited or acquired deficiency in the complement regulatory system, we agree with the recommendation of empiric early initiation of plasmapheresis for patients presenting with non-Shiga toxin, nonpneumococcal-associated HUS. We accept that we will inevitably be treating a percentage of these patients who may have an acute, nonrecurring condition. Given that genetic mutation analysis may take months, we also agree with the early use of eculizumab for those patients with clinical, pathologic, and/or molecular features suggestive of an inherited disorder especially if they have any of the following: a positive family history (nonsimultaneous) of HUS, recurrent HUS, or hypocomplementemia at presentation. For all other patients, we suggest that eculizumab be reserved for those patients with failure to respond to plasmapheresis after 3 to 5 days. We offer this recommendation as it is often more difficult to stop a therapy once it is started (such as eculizumab), as it impossible to know if a patient's recovery was due to the intervention or the natural course of the disease. We acknowledge that patient 1 had transiently low C3 and C4 levels at presentation. At the time, eculizumab was not readily available for use. If this patient had presented now, we may have considered using eculizumab and we would not have known whether her recovery was related to the treatment or the natural progression of her disease.

To our knowledge, this is the first report of an acute, resolving nondiarrheal HUS phenotype in the era of molecular and genetic testing for disorders of complement regulation. All three patients had the HUS phenotype including thrombocytopenia, microangiopathic hemolytic anemia, and AKI. None had Shiga toxin infection, none had evidence of *S. pneumoniae* infection, and none had a prior history of HUS or a family history of HUS. All three had severe renal involvement requiring acute dialysis. All were treated with plasmapheresis or plasma infusions. In two patients, there was no evidence of thrombotic microangiopathy on renal biopsy. Although the finding of thrombotic microangiopathy contributes to the diagnosis, HUS remains a clinical syndrome defined by the triad of anemia, thrombocytopenia, and AKI, and not by biopsy findings. In actuality, many patients with HUS never have a pathologic or tissue diagnosis, and clinicians are left to make decisions about therapy based on clinical grounds alone. All three patients made complete recovery and none has had recurrence of disease. In addition, two of the patients had unusual extrarenal manifestations (liver failure and transverse myelitis) not typically associated with the genetic or recurrent forms of HUS. For patient 2, it is possible that the same process that caused transverse myelitis also led to HUS, although we cannot know if HUS was triggered by one of the therapies she received or unrelated altogether.

These patients contribute to the current literature that illustrates the significant heterogeneity and phenotypic diversity of atypical HUS. A grim prognosis may not be in order for all of these patients with HUS, and treatment should be carefully considered prior to the use of long-term plasma therapy and/or eculizumab.

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