Multifaceted Hemolytic Uremic Syndrome in Pediatrics

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Key Words

Hemolytic uremic syndrome • STEC HUS • Atypical hemolytic uremic syndrome • Complement

Abstract

Hemolytic uremic syndromes can have devastating consequences in childhood. The common feature of a microangiopathic hemolytic anemia and thrombocytopenia associated with varying degrees of renal injury often creates diagnostic confusion. The inability to arrive at a definitive diagnosis quickly can lead to a delay in initiating renal-preserving and sometimes life-saving treatment. Currently, both the treatment plan and the prognosis vary substantially according to the presumed diagnosis. The availability of anti-complement therapy makes differentiating the cause of the hemolytic uremic syndrome particularly critical. Therefore, it is imperative that consideration be given to each of the possible syndromes at presentation in order to facilitate correct diagnosis and development of an appropriate treatment strategy for both the acute phase and for the long-term care of the patient.

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Introduction

The presentation of a microangiopathic hemolytic anemia, thrombocytopenia and renal impairment in childhood points to the diagnosis of one of the hemolytic uremic syndromes (HUSs). Collectively, the syndromes are characterized by a typical pathological lesion: endothelial cell swelling, subendothelial accumulation of cellular debris and platelet-rich thrombi. This pathological lesion leads to vascular lumen obstruction, provoking organ ischemia and the myriad of symptoms that are seen in HUS. The fact that each of these syndromes results from a near identical pathological lesion results in clinical overlap that can contribute to diagnostic confusion. Both the treatment plan and the prognosis vary substantially according to the presumed diagnosis. Therefore it is imperative that consideration be given to each of the possible syndromes at presentation in order to facilitate correct diagnosis and development of an appropriate treatment strategy in both the acute and long-term setting.

Historically, the HUSs in children have been classified as either *diarrhea-positive* versus *diarrhea-negative* or as *typical* versus *atypical*. These designations have now been supplanted by terms that are meant to be more descrip-

tive and include STEC HUS (for Shiga toxin-producing *Escherichia coli*) and complement-mediated HUS as well as multiple secondary forms that are referred to by their associated pathology (i.e. streptococcal-associated HUS, malignant hypertension-associated HUS, etc.) (table 1). Though the renal microvasculature is the predominant site of the pathological lesion in HUS, the vasculature of other organs are frequently involved and may play a significant role in the morbidity for any given patient. A brief overview of the syndromes is presented below.

STEC HUS

Pathophysiology

Shiga toxin (Stx) infection is a classic example of an infection that can induce a microangiopathic hemolytic anemia with thrombocytopenia. Bloody diarrhea is often the first clinical sign of disease and will not only be the clue to an inciting infection but will be the trigger for the necessary laboratories to facilitate a firm diagnosis. When acute kidney injury also occurs, the triad for the diagnosis of an HUS has been met and it becomes appropriate to define the patient as having STEC HUS.

The vast majority (~80%) of individuals with STEC infection experience a self-limited course of gastrointestinal symptoms and do not progress to the systemic symptoms of HUS [1, 2]. The factors predisposing patients with STEC infection to the systemic syndrome of STEC HUS remains unclear.

Escherichia coli O157:H7 (also referred to as enterohemorrhagic *E. coli* – EHEC) is the prototypical pathogen known to cause STEC HUS in the United States, however *Shigella* and other *E. coli* have also been associated with disease in other settings [3–5]. The incidence of STEC HUS is estimated to be 1–2 cases/100,000 per year, with most pediatric diagnoses occurring in patients under age 5 years [6, 7]. The relative frequency of STEC HUS requires that it be the primary consideration when approaching the child with HUS.

The pathophysiology of STEC HUS relates to the biological characteristics of the causative organisms and the toxins they express. Following ingestion, non-invasive EHEC colonize the terminal ileum and releases Stx [8, 9]. The ability to infect and cause death of enterocytes as well as trigger systemic intravascular effects is a direct consequence of the Stx. Stx binds to specific receptors distributed throughout endothelial cells of the gastrointestinal tract, pancreas, brain, and kidney and is responsible for a multitude of cytotoxic, proinflammatory and

Table 1. HUSs that can present in childhood – a comprehensive laboratory workup is designed to distinguish these entities from one another, particularly when the clinical presentation is not straightforward

STEC HUS (typical or diarrhea-positive HUS)
Toxin associated
Secondary HUS
Streptococcal infection associated
Malignant hypertension associated
Pancreatitis associated
Medication associated
Transplant related
Autoimmune disorder associated
Cobalamin disorder associated
Septicemia or DIC associated
Malignancy associated
Pregnancy associated (HELLP)
Complement-mediated HUS (atypical or diarrhea-negative HUS)
Alternate complement pathway gene abnormality
Idiopathic

prothrombotic effects [10]. Systemic complications resulting from Stx include cell death, platelet activation and deposition, cytokine release and increased tissue factor expression on the cells of the microvasculature [11]. Microthrombi formation in the microvasculature following Stx-induced platelet activation results in the abnormal shear stress and disturbances in blood flow that eventually leads to the production of the fragmented red blood cells or schistocytes representative of a microangiopathic anemia.

Clinical Manifestations and Diagnosis

Children with STEC HUS classically present with bloody diarrhea and then are found to have a microangiopathic anemia (often associated with an elevated lactic acid dehydrogenase and a decreased haptoglobin with no signs of autoimmunity), thrombocytopenia and acute kidney injury as evidenced by elevation of serum creatinine above the upper limit for age. It is important to note that while more than 90% of children with STEC HUS will experience bloody diarrhea, a subset of patients will not [1]. The enteric prodrome often lasts 4–7 days prior to the development of STEC HUS. Stool culture positivity for Stx-producing *E. coli* aids in diagnosis, however a negative stool culture does not rule out STEC HUS in the presence of the above classical presentation. Thrombocytopenia is the first blood abnormality often present in patients and is subsequently followed by hemolysis and

anemia precipitated by the small vessel thrombi [1]. Other symptoms of STEC HUS include oligoanuria, neurological dysfunction (ranging from transient ischemic attacks to seizures), pancreatitis, and elevated liver enzymes. Fever may be present in STEC HUS. Metabolic abnormalities are common and include hyperkalemia, hyponatremia, and hyperuricemia. Severe hemorrhagic colitis may lead to gangrenous colitis [12], bowel perforation, and sepsis in the most severe cases [13].

Acute kidney injury is a classic component of STEC HUS and occurs presumably due to the binding of Stx to its receptor on the glomerular basement membrane. Both glomerular injury and tubular injury in the form of acute tubular necrosis are common findings in STEC HUS [14, 15]. Cortical necrosis may occur in severe cases of STEC HUS. Neurologic symptoms including irritability, seizure and stroke are also reported in STEC HUS [16–18].

Treatment

Treatment for STEC HUS is largely supportive with the intent to normalize blood pressure, restore intravascular volume, recover electrolyte abnormalities, and maintain adequate nutrition. Gastrointestinal pain may be prominent and require either acetaminophen or even judicious use of morphine [19]. Patients may require transfusion of packed RBCs, however a clear threshold for transfusion has not been studied [6]. Platelet transfusions are not typical and are reserved for active bleeding or when preparing for an invasive procedure such as a catheter placement [13].

Key to the treatment of STEC HUS and prevention of renal complications is early fluid resuscitation and volume expansion. Current treatment using aggressive isotonic volume expansion is based on a protocol designed by Tarr et al. [19]. Crystalloid fluids should be administered in 20 ml/kg boluses until euvolemia is achieved and then subsequent fluid management is based on nutritional needs balanced against output [19].

Though case reports exist to demonstrate marginal effectiveness of plasma therapy in STEC HUS, there remains no clear role for plasma therapy in STEC HUS [20, 21].

Renal replacement therapy may be required for some patients. Indications for dialysis parallel that of acute kidney injury of any cause: hyperkalemia, oligoanuria, uremia, metabolic acidosis, and/or volume overload. Both hemodialysis and peritoneal dialysis are suitable options [13]. Continuous renal replacement therapy may also be employed for more unstable patients with multiorgan involvement, severe fluid overload, or cardiovascular instability.

Antibiotic treatment for the prevention of typical HUS in children with STEC has not been shown to be effective. Specifically, literature has shown use of antibiotics such as fluoroquinolones and sulfa drugs to be more harmful than beneficial [13, 22, 23].

Recently there has been interest in using anti-complement therapy (specifically eculizumab an anti-C5 antibody) in those patients with severe neurologic involvement [24]. The large outbreak of STEC HUS caused by *E. coli* O104:H4 that occurred in Germany in May 2011 tested this potential intervention. Eculizumab was used in a number of patients. The data are conflicting, however the bulk of the published data on HUS [25, 26] suggests that there are no short-term benefits of eculizumab in comparison to therapeutic plasma exchange in the treatment of STEC HUS. Therefore the role of eculizumab in this toxin-mediated disease remains unclear.

Prognosis

More than 80–90% of patients with STEC infection have a self-limited course, however those who develop typical HUS may require intensive care. Long-term sequelae may be present in up to 20% of children with typical HUS including chronic kidney disease, hypertension, diabetes, and neurological impairment [16, 26]. Acute mortality from typical HUS is between 1 and 4% [1, 16].

Atypical HUS

Pathophysiology

Atypical HUS (aHUS) is defined also as a microangiopathic anemia with thrombocytopenia and renal failure, however in this case there is most often (though not exclusively) no classic enteric prodrome [6, 27]. aHUS is caused by abnormalities in the alternate complement pathway (AP), resulting in uncontrolled complement activation and subsequent tissue damage.

The AP is constitutively active and functions as an arm of our innate immune system. Tight control of the AP is required to limit unregulated generation of both anaphylatoxins and the membrane attack complex [28]. Dysregulation of the alternate pathway of complement at the vascular endothelial cell surface results in the classic endothelial cell damage, platelet activation and thrombus formation that is seen in the other HUSs.

It has been shown that mutations in genes encoding proteins that regulate the AP or autoantibodies that inhibit AP complement regulatory proteins can be identified in approximately 60–70% of aHUS patients [29, 30]. Both

Table 2. Laboratory evaluation of a patient with suspected HUS – these laboratory studies may be modified based on the patient's clinical presentation

R/O STEC HUS	Stool or rectal swab: culture for STEC; PCR for Stx serum: antibody testing
R/O <i>Streptococcus pneumoniae</i> infection	Blood cultures, pulmonary cultures
R/O thrombotic thrombocytopenia purpura	Plasma ADAMTS13 activity $\pm$ inhibitor
R/O other secondary causes of TMA	Malignant hypertension, pancreatitis, malignancy, medication
R/O cobalamin metabolism abnormality (i.e. methylmalonic aciduria)	Homocysteine, methionine, urine organic acid testing
R/O rheumatologic disease	Consider genetic testing for mutation in MMACHC gene
R/O HIV	Antinuclear antibody, lupus anticoagulant, anti-phospholipid antibodies
R/O pregnancy-associated TMA/HELLP syndrome	HIV serology
R/O complement pathway abnormality	Pregnancy test, liver enzymes. C3, factor H, factor I, factor B serology Anti-factor H autoantibodies MCP – surface expression on leukocytes by FACS Gene mutation analysis for CFH, CFI, CFB, C3, CFHR5, MCP, evaluation for fusion proteins and CFHR1/3 deletion

mutations that result in a quantitative deficiency of protein and mutations associated with a normal plasma level of functionally ineffective protein have been identified.

Complement factor H (CFH) mutations are the most common and account for 23–27% of identified mutations in registry patients in the USA and Europe [7, 8]. Membrane cofactor protein (MCP) mutations occur at a frequency of 5–7%. Complement factor I (CFI) and complement component C3 (C3) occur at 4–8 and 2–8% respectively. Gene mutations in complement factor B (CFB) and thrombomodulin (THBD) have also been noted (1–4 and 3–5%) [31, 32].

The CFH-related proteins (CFHR) have also been associated with aHUS. In addition, non-allelic homologous recombination in the CFH and CFHR region results in hybrid proteins that are often poorly functioning and may affect the regulatory role of the native CFH protein. These mutations account for 1–3% of aHUS patients [30]. Finally, 6–10% of patients have an acquired risk for aHUS via anti-CFH [30, 33, 34].

35–40% of individuals with a clinical scenario consistent with aHUS will have no demonstrable genetic mutation using current screening strategies. To further complicate this scenario, even when genetics are well described in a given family, the penetrance of disease is only 50% – with half of the family members with the same mutation remaining healthy [35].

aHUS is associated with a variety of disease triggers including organ transplantation, immunomodulatory agents and antiplatelet drugs [36–38]. Specifically an association between renal transplant, calcineurin inhibitor

therapy, and humoral graft rejection [39–41] has been reported. Interestingly, 10–15% of aHUS cases appear to occur in conjunction with pregnancy or in the postpartum period [6].

Clinical Manifestations and Diagnosis

An estimated 10% of all HUS cases are classified as atypical or complement-mediated and are not associated with Stx [6, 42]. Acute aHUS episodes are uncommonly associated with an enteric prodrome and classically manifest in severe hemolytic anemia, thrombocytopenia, and acute kidney injury [6]. In contrast to STEC HUS, aHUS may be precipitated by illness such as fever, upper respiratory tract infection, and non-bloody diarrhea. There have been reports of 0157:H7 *E. coli* triggering aHUS in pediatric patients with defined mutations [43]. Extrarenal, specifically central nervous system or visceral involvement, occurs in approximately 10–20% of patients [37, 43]. Recurrent, HUS should trigger the concern for aHUS [27]. The majority of patients will present their first episode of aHUS as a child [44, 45].

The diagnosis of aHUS requires that the clinician rule out potential confounding diagnoses (table 1). Most importantly, the patient must not meet criteria for STEC HUS and not meet criteria for thrombotic thrombocytopenia purpura. Current recommendations suggest that patients suspected of aHUS may require several laboratory screening studies (table 2) in order to rule out alternative HUS diagnoses. The goal is to arrive at an accurate diagnosis such that an appropriate therapy can be chosen.

Fig. 1. An algorithm for the use of plasma therapy or the treatment of aHUS.

Treatment

As with STEC HUS, symptomatic management of volume, anemia and renal sequelae (e.g. normalization of blood pressure) should be a primary focus when aHUS is suspected. In conjunction with symptomatic care, plasma therapy (either exchange or infusion) has been the mainstay of acute therapy for aHUS. Although no randomized controlled trials have been completed to date, plasma exchange has been associated with at least a 25% decrease in mortality [46]. Plasma therapy should ideally be started within 24 h after establishing a presumed diagnosis of aHUS [20]. Current recommendations suggest initiating exchange of 1.5 times plasma volumes with fresh frozen plasma or fresh frozen plasma mixed with albumin (approximately 65–70 ml/kg) per session (fig. 1). Exchange should begin as a daily procedure for 5 days followed by 5 days per week for 2 weeks, and finally 3 times per week for 2 weeks [20]. Plasma therapy can then be reduced based on the patient's clinical response. It is unclear whether anticellular immunosuppressive agents must also be added to those patients that have anti-CFH antibodies in order to achieve remission [45]. Resolution of renal sequelae and hematologic normalization, resulting in either complete or partial remission, can occur in up to 60% of patients undergoing plasma exchange therapy [44, 45].

Trials using the anti-complement drug eculizumab have now been completed and the results reported in abstract form have been promising [47, 48]. Published case studies and the adult and adolescent trial data abstracts suggests that eculizumab may be superior to plasma exchange for halting the hemolytic process [49]. Taken together, evidence suggests that eculizumab should be considered as an alternate initial treatment for aHUS. As with plasma therapy, if eculizumab is to be used for aHUS, it should be started as soon as possible to limit irreversible organ injury. Treatment doses are provided by the manufacturer. The duration of therapy continues to be debated.

When genetic mutation of one of the alternate pathway proteins produced in the liver is present, liver transplant may be an option. Liver transplantation has the potential to provide the physiologic means to correct the underlying genetic defect and prevent recurrence [50].

Prognosis

Until very recently, prognosis for aHUS has been poor. aHUS has been associated with death rates as high as 25% [42] and progression to ESRD in approximately 50% of patients [6, 51]. Nearly 60–70% of all patients with mutations in *CFH*, *CFI*, or *C3* mutations have relapsed or suffered end-stage renal disease within the first year of diagnosis, lost renal function during the presenting episode,

or died during the presenting episode [41, 45]. The introduction of anti-complement therapy for the treatment of aHUS is likely to alter the history of aHUS however to what extent remains to be seen.

When ESRD occurs and a renal transplant is undertaken, a high disease recurrence rate has been found (50%) and the graft failure rate with recurrence has been 80–90%. Protocols are now available to improve renal transplant outcome and they generally include both plasma therapy and eculizumab [52].

Secondary HUS

Lastly, there remains a subset of microangiopathic hemolytic anemias that do not fit into the above two classifications (table 1). These microangiopathies are known as the secondary HUSs and are typically named in association with the presumed precipitating disease (i.e. lupus-associated HUS or calcineurin inhibitor-associated HUS, etc.). This category includes all those diseases that cause HUS as a secondary phenomenon. Secondary HUSs have been described in association with a wide variety of diseases (most of which have either no or an unclear association with the AP) including non-STEC infectious agents (*Streptococcus pneumonia* and HIV), ma-

lignancy, chemotherapy, bone marrow or solid organ transplantation, calcineurin inhibitors, pregnancy, malignant hypertension, systemic lupus erythematosus and other rheumatologic diseases and disorders of cobalamin metabolism [6, 37, 53–55]. In general, the treatment for a secondary HUS is to treat the primary disorder and support the patient with fluid, blood or antihypertensive therapy as necessary. There are no data to support a more specific treatment of this type of microangiopathy at this time and it remains unclear whether anti-complement therapy may be useful in this setting.

In conclusion, the thrombotic microangiopathies are a heterogeneous group of diseases with similar presenting characteristics that have both different etiologic mechanisms and different ideal treatment regimens. Despite the absence of specific markers to distinguish these diseases and the difficulty in separating them clinically, it is nonetheless supremely important to attempt to categorize the HUSs according to one of these subsets in order to deliver optimal care.

Disclosure Statement

Dr. Nester is on Alexion Pharmaceutical's International Advisory Board for Atypical Hemolytic Uremic Syndrome.

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