Hemolytic Uremic Syndrome

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ABSTRACT

Although patients with the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have similar pathological lesions affecting the small blood vessels, they have different (but sometimes overlapping) clinical features and treatment strategies and prognosis. With the recent demonstration of an inherited or acquired enzyme deficiency that underlies patients with TTP, the classification of patients into the 'HUS-TTP syndrome' is proposed to be changed, with the diagnosis of TTP reserved for patients with the enzymatic defect and HUS for the rest of the patients with microangiopathy and classical pathology. HUS is classified into diarrhoea associated (D+) and non-diarrhoeal (D-) forms. D+HUS mainly affects children, and in the Western world follows infection by enterohemorrhagic *E.coli*. In India, *Shigella dysenteriae* infection is the commonest cause of childhood D+ HUS. The diagnosis can be confirmed by the presence of thrombocytopenia and schistocytes in the peripheral smear. Patient with the diarrhea-associated HUS generally has a good prognosis and recovers with supportive treatment only, without much long term sequelae. In contrast, patients with adult-onset HUS, as well as those with TTP have a worse prognosis and require specific treatment including plasma exchange/infusion to produce disease remission and are at a higher risk of long-term sequelae. Patients with irreversible renal failure can undergo kidney transplantation; however the disease can recur in the transplanted kidney.

INTRODUCTION

In 1952, Symmers first introduced the term thrombotic microangiopathy (TMA), to describe vessel wall thickening affecting mainly arterioles and capillaries with detachment of the endothelial cell from the basement membrane, accumulation of fluffy material in the subendothelial space, intraluminal platelet thrombosis, and partial or complete obliteration of the vessel lumina.[1] In patients with TMA lesions, laboratory features of thrombocytopenia and hemolytic anemia are almost invariably present, and these reflect consumption and destruction of platelets and red blood cells in the microvasculature.

Depending on whether renal or brain lesions were predominant, two pathologically indistinguishable, but clinically different entities were described. They were termed as hemolytic uremic syndrome (HUS), after the children with hemolytic anemia, thrombocytopenia and acute renal failure reported by Gasser et al in 1955,[2] or as thrombotic thrombocytopenic purpura (TTP), when the neurological symptoms were predominant after the case reported by Moschowitz in 1923.[3] In some patients, both neurologic abnormalities (such as seizures and coma) and acute renal failure occurred and such patients were described by the comprehensive term TTP-HUS. However, with the recent identification of an enzyme deficiency in patients with TTP (see below), the emphasis for differentiating HUS from TTP has shifted from the pattern of clinical involvement to the presence or absence of the enzyme deficiency. It is now suggested that the diagnosis of TTP should be used to describe only those patients who have this enzyme deficiency; while patients without the enzyme deficiency should be labeled as suffering from HUS.[4]

ETIOLOGY AND PATHOGENESIS

Although many cases of HUS/TTP are idiopathic, several underlying causes have been identified and are listed in Table 1.

Most cases of childhood HUS and occasional cases in adults follow infection by enterohemorrhagic *E.coli* (typically *E.coli* 0157:H7). A toxin released from these bacteria is responsible for the manifestations and since it is identical to the toxin produced by *Shigella dysenteriae*, it is called Shiga toxin (Stx). The toxin has a predilection for the renal circulation since receptors for it are preferentially expressed in the kidney. Both endothelial injury and activation of platelets and neutrophils may contribute to Stx-induced HUS. The toxin can also cause apoptosis and significant damage to renal tubular epithelial cells.[5]

Autosomal recessive and dominant forms of familial HUS comprise less than 5% of all cases of HUS. Mutations in the gene for factor H, a serum complement regulatory protease, account for some of these. This gene is located on chromosome 1q32.

Table 1: Causes of HUS/TTP

Childhood HUS
Following severe diarrhea with 0157:H7 *E.coli*
Idiopathic (rare)
Adult TTP/HUS syndromes
Idiopathic
Drug toxicity
Cancer chemotherapy
Mitomycin C
Bleomycin and cisplatin
Gemcitabine
Cyclosporine and tacrolimus
OKT_3 monoclonal antibody
Immune-mediated
Quinine
Ticlopidine and clopidogrel
Conditioning for bone marrow transplantation
Pregnancy or postpartum
Autoimmune disease
Antiphospholipid antibody syndrome
Systemic lupus erythematosus
Scleroderma
AIDS and early symptomatic HIV infection

Serum C3 levels are low in such patients both when the disease is active as well as during remission. The presence of low C3 levels may also help identify family members at risk for the disease. It is, however, not clear how deficiency of this factor predisposes to HUS. More than 50% of those with familial HUS have repeated recurrences of the disease.[5,6]

Another factor that may underline platelet aggregation in HUS is plasminogen activator inhibitor (PAI-1). Increased levels of PAI-1 have been found in children with post-diarrhoeal HUS. It is not clear; however, if the enhanced release of PAI-1 is a primary response or is secondary to endothelial injury.[7]

Low complement (C3) levels are well known to accompany the acute phase of diarrhoea associated and idiopathic HUS and probably reflect C3 consumption in the microvasculature. Granular C3 deposits in glomeruli and arterioles of HUS patients and C3 breakdown products in HUS sera further confirm the activation of the complement system in the acute phase of the disease.[5,6]

In patients with TTP, the mechanism causing platelet consumption appears to be different and can distinguish it from HUS.[4,8] Von Willebrand factor (VWf) is synthesized in endothelial cells and assembled in larger multimers that are present in normal plasma. The larger multimers, called unusually large Von Willebrand factor (ULVWf), are rapidly degraded in the circulation into the normal size range of VWf multimers by a specific von Willebrand factor-cleaving protease (or cleaving metalloproteinase, now also called ADAMTS13: a disintegrin-like and metalloprotease with thrombospondin type 1 repeats). ULVWf multimers (including unique forms arising from proteolytic digestion) accumulate in patients with TTP, being found in the platelet thrombi and serum. These ULVWf multimers can attach to activated platelets, thereby promoting platelet aggregation. ULVWf multimer accumulation in TTP is associated with absent or markedly diminished ADAMTS13 activity due to an inherited or acquired deficiency.[8] Mutations in a gene on chromosome 9q34 are associated with this deficiency. An inhibitory autoantibody to the metalloproteinase has been found among a high percentage of patients with the acquired forms of TTP. In contrast, ADAMTS13 deficiency is not seen in patients with HUS.[4]

CLINICAL FEATURES

Childhood HUS

Childhood HUS, which is usually a diarrhea-associated (D+HUS), is most often due to *E.coli* O157: H7 infection in the Western world while *Shigella dysenteriae* is the commonest cause in India. It is characterized by a prodromal phase of diarrhea followed by acute renal failure. The peak incidence is in children younger than five years of age. *E.coli* 0157 infection is most common in the summer months. The average interval between *E.coli* exposure and illness is three (range of 1 to 8) days. The illness typically begins with abdominal cramps and non-bloody diarrhea; diarrhea may become hemorrhagic in 70% of cases usually within one or two days. Vomiting occurs in 30 to 60% of cases and 30% may have fever. Superficial ulcerations or pseudomembranes are common. *E.coli* 0157 infection is complicated by HUS in 3 to 7% of the sporadic cases and up to 20% of the epidemic forms. The diagnosis of HUS is usually made after an average of six days after the onset of diarrhoea once renal failure supervenes.[5] Renal involvement presents with oligoanuria and is often associated with hypertension. Microscopic hematuria and mild proteinuria are common and rarely gross hematuria may also occur.

Adult HUS

Adults usually have HUS that is not preceded by a prodrome of diarrhoea (D-HUS). The other manifestations are the same as in children but renal involvement is more severe and more frequently associated with sequelae.[5] Rarely, HUS may occur following enterohemorrhagic *E.coli* infection as in children.

LABORATORY FINDINGS

Thrombocytopenia and microangiopathic hemolytic anemia are the laboratory hallmarks of HUS/TTP. Thrombocytopenia is usually severe, with platelet counts below 60,000/mm^3 in most cases. Thrombocytopenia may be transient and less severe in those who have renal failure. Giant platelets may also be seen in the peripheral smear.

Anemia is usually severe with hemoglobin levels less than 6.5 gm/dL in 40% of cases. A neutrophilic leukocytosis is common in childhood HUS. Serum lactate dehydrogenase levels (LDH) are markedly increased. Hyperbilirubinemia (mainly conjugated), reticulocytosis, circulating free hemoglobin, and low or undetectable haptoglobin levels are additional indicators of hemolysis. Detection of fragmented red blood cells (schistocytes) in the peripheral smear together with a negative Coombs' test confirms the microangiopathic nature of the hemolysis. A schistocyte count of >1% is strongly suggestive of HUS. Urine microscopy may show red cells and rarely red cell casts and hypocomplementemia occurs in 50% of patients. Renal biopsy may be helpful in selected patients in whom the diagnosis is

uncertain and can also predict the outcome. However it can be done only after reversal of thrombocytopenia.

HUS/TTP can be distinguished from disseminated intravascular coagulation by normal levels of coagulation components and absence of prolongation of the prothrombin time and partial thromboplastin time. The antiphospholipid antibody syndrome which may also cause similar clinical manifestations also prolongs the partial thromboplastin time.

PATHOLOGY

The characteristic histologic lesions of HUS and TTP consist of wall thickening of capillaries and arterioles with swelling and detachment of the endothelial cells from the vascular basement membrane and accumulation of fluffy material in the subendothelium. These changes are virtually identical and often indistinguishable from the microvascular lesions of scleroderma and malignant hypertension. In HUS, the microthrombi are confined primarily to the kidneys. TTP mainly involves the brain and the intravascular thrombi apparently form and disperse repeatedly, producing intermittent neurological signs. In pediatric patients, particularly in children with Stx-associated HUS, glomerular injury is prominent. Leukocyte infiltrates and thrombi are common during the early phases of the disease and usually resolve over two or three weeks. Later on, renal biopsies show ectatic glomerular capillaries, swollen endothelial cells and some degree of necrosis. Patchy cortical necrosis may be seen in more severe cases. Predominant arteriolar involvement, with intimal proliferation and hyperplasia, and secondary glomerular ischemia and collapse are frequently found in idiopathic and familial forms and in older children. Prognosis is good in cases with predominantly glomerular changes (as seen in D+HUS), but is much worse in those with primary vascular damage with or without acute cortical necrosis (as seen in D-HUS). Pure glomerular involvement is uncommon in adults. Vascular involvement is the predominant finding and is associated with more severe hypertension, more frequent neurological involvement, higher risk of renal and neurological sequelae, and higher mortality.[5]

TREATMENT GUIDELINES

Childhood HUS

Childhood Stx-*E.coli* associated HUS usually recovers spontaneously with supportive therapy and may not require any specific therapy. The mortality rate from this condition has significantly decreased over the last 40 years from 40 to 50% to 5%, probably as the result of better supportive management of anemia, renal failure, hypertension, and electrolyte and water imbalance. Up to 50% of patients may need dialysis and 75% could require red blood cell transfusions. However, no specific therapy aimed to prevent or limit the microangiopathic process has been proven to affect the course of the disease in children with D+HUS. However, in the minority of children who have persistence of the microangiopathic process, plasma exchange may be tried.

Antimotility agents may increase the risk of toxic megacolon. Antibiotics given to treat infection due to Stx-producing *E.coli* 0157:H7 have been found to increase the risk of overt HUS by 17-fold.[9] Indeed, antibiotic-induced injury to the bacterial membrane might favor the release of large amounts of preformed toxin. Alternatively, antibiotic therapy might give *E.coli* 0157:H7 a selective advantage if these organisms are not as readily eradicated from the bowel as are the normal intestinal flora. Moreover, several antimicrobial drugs, particularly the quinolones, trimethoprim, and furazolidone, are potent inducers of the expression of the Stx 2 gene and may increase the level of toxin in the intestine.[10]

Several new agents targeted to prevent organ exposure to Stx are currently under evaluation. The most promising are Synsorb-PK, a resin composed of repeated synthetic carbohydrate determinants linked to colloidal silica that binds Stx; recombinant modified *E.coli* that display a Stx receptor mimic on its surface and adsorbs and neutralizes Stx; and "Starfish", an oligovalent , water-soluble carbohydrate ligand that can simultaneously engage all five B subunits of two toxin molecules. Preliminary analyses have found that early treatment (within two days after the onset of diarrhoea) with Synsorb-PK decreases the risk of HUS from 17 to 7%.[11]

Adult HUS/TTP

A general consensus has been achieved that plasma exchange or infusion should always be tried in adult patients with HUS/TTP to minimize the risk of death or long-term sequelae. Plasma exchange has been claimed to be superior to plasma infusion in one study.[12] However, patients treated with plasma exchange were given larger amounts of plasma than those treated with plasma infusion alone. Indeed, when equivalent volumes of plasma were given, infusion and exchange appeared to be equally effective.[13] Therefore, plasma exchange should be considered as first-choice therapy when renal insufficiency or heart failure limit the amount of plasma that can be provided with infusion alone.

Cryosupernatant fraction i.e., plasma from which a cryoprecipitate containing the largest plasma vWF multimers, fibrinogen, and fibronectin has been removed has been successful in treating patients who did not respond to repeated exchanges or infusions with fresh frozen plasma.[14] Plasma cryosupernatant may provide the same beneficial factor(s) found in whole plasma but does not contain those factors (including large vWF multimers) that may actually sustain the microangiopathic process until remission is achieved.[5]

Usually one plasma volume (40 ml/kg) is exchanged daily. Treatment can be intensified by increasing the volume of plasma replaced. On the average, 7-16 daily exchanges are required. Patients with the hereditary form of TTP who have deficiency of ADAMTS13 typically respond to lower doses of plasma infusion (i.e., 10-15 ml/kg), because a low level of ADAMTS13 activity obtained from the infused plasma is sufficient to induce remission of the microangiopathic process. This is in contrast to patients with the acquired form of TTP (with inhibitors of ADAMTS13), who require large amounts of plasma to achieve remission.[4]

Serum LDH and platelet count are the most reliable markers of response, and plasma therapy should be continued until they have persistently normalized. When a normal platelet count has been achieved, plasma exchange is gradually tapered by increasing the interval between treatments. Occasional patients with idiopathic

HUS/TTP do not achieve remission despite plasma therapy. Some of them become plasma-dependent and require continued treatment, since disease relapses as soon as plasma infusion or exchange is stopped. Improvement in renal function also occurs but is unpredictable. Even those who require dialysis during the acute episode can recover sufficient function to stop dialysis. Persistent hypertension and impairment of renal function are common and do not indicate active disease or the need for continued plasma exchange.

Splenectomy has been found to induce remission in some plasma-resistant cases, but was ineffective and actually increased morbidity and mortality in others.[15] Platelet transfusions are best avoided as they may fuel the thrombotic process,[15] and their use is recommended only in patients with thrombocytopenia and active bleeding or before performing invasive procedures.

In patients with irreversible renal failure, renal transplantation can be done. Transplantation is however contraindicated in those with familial relapsing forms of HUS because of the high risk of recurrence affecting the transplant.

Secondary HUS/TTP

Patients with drug-induced HUS/TTP usually promptly recover after drug withdrawal. Plasma exchange is ineffective in mitomycin C-induced disease but with drugs like quinine, the disease is so severe that plasma therapy seems mandatory. In ticlopidine-induced HUS also, the mortality rate in those receiving plasma exchange is significantly lower than in those who do not receive this treatment. Pregnancy associated HUS should also be treated by plasma therapy.[5] Cases recurring after a kidney transplant are almost invariably found in the context of a familial HUS and are associated with a poor outcome. In post-transplant HUS associated with cyclosporine A or tacrolimus therapy, withdrawal of the drug and plasma therapy can cure the disease.

LONG TERM SEQUELAE

Long-term renal sequelae of HUS are common. Ten to 42% of children have some sequelae such as proteinuria and/ or moderate hypertension or mildly reduced GFR, 10 to 22% have chronic renal failure, and 2 to 9% ESRD. The duration of anuria is a strong predictor of persistent renal dysfunction. Indeed, only 4 of 53 children (7.5%) with a duration of anuria less than 10 days were found to have a residual GFR <80 mL/min as compared with 15 of 35 (42.8%) of those with anuria duration >16 days.[16] The extent of acute structural injury and loss of functioning nephron units may account for long- term sequelae of the disease. At 15 years of follow up, Gagnadoux et al found renal sequelae in 83% of children with patchy cortical necrosis, one-third of whom were in ESRD, as compared with none of those with pure glomerular TMA.[16]

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