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A Mechanistic Approach to the Diagnosis and Management of Atypical Hemolytic Uremic Syndrome

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ABSTRACT

Until recently, atypical hemolytic uremic syndrome (aHUS), conventionally defined in the pediatric literature as a syndrome of the triad of renal failure, microangiopathic hemolytic anemia, and thrombocytopenia without a prodrome of hemorrhagic diarrhea, has received little attention in adult practice because the patients are commonly given the diagnosis of thrombotic thrombocytopenic purpura (TTP) or TTP/HUS and treated as TTP with plasma exchange, augmented in refractory cases with rituximab and sometimes even splenectomy. Molecular studies have shown that the regulation of the alternative complement pathway is defective in many patients with conventionally defined aHUS. With this new knowledge and the findings of ADAMTS13 autoinhibitors or mutations in TTP, it is time to redefine aHUS as a disorder with propensity to the development of thrombotic microangiopathy due to defective regulation of the alternative complement pathway and TTP as a disorder with propensity to arteriolar and capillary thrombosis due to ADAMTS13 deficiency. This new definition provides a clear distinction of aHUS from TTP, encompasses patients without all 3 components of the triad, and provides the rationale for management with anticomplement therapy.

Contents

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Atypical hemolytic uremic syndrome (aHUS) originally refers to the triad of renal failure, microangiopathic hemolytic anemia (MAHA), and thrombocytopenia without a prodrome of hemorrhagic diarrhea [1,2]. Until recently, the diagnosis of aHUS has been used primarily in pediatric literature, as most children presenting with MAHA and thrombocytopenia also have renal failure. In adult practice, thrombotic thrombocytopenic purpura (TTP) is a better known disorder and patients with renal failure are often considered to have TTP/HUS or simply TTP [3].

With the discovery of ADAMTS13 deficiency in a subset of patients with "TTP," questions have been raised on the appropriateness of this diagnosis for patients who do not have ADAMTS13 deficiency. Most of the patients without ADAMTS13 deficiency have prominent renal failure [4] and would have been given the diagnosis aHUS if the pediatric criteria were used. However, surprisingly, in a scheme of disease classification, there was no aHUS for adult patients [3].

Molecular and genetic studies have detected evidence of defective regulation of the alternative complement pathway in many cases of aHUS, including adult 'TTP' cases without ADAMTS13 deficiency [5]. These findings provided the rationale for 2 clinical trials to assess the role of eculizumab, a humanized monoclonal antibody of complement C5, in the treatment of aHUS. These trials, although not randomized, show that the anticomplement therapy is highly effective both for patients with active disease not responding to plasma therapy and for patients requiring maintenance plasma therapy to prevent relapses [6]. These results led to fast-track approval of eculizumab for aHUS in the United States and European Union in 2011 and in Canada in 2013.

Until recently, aHUS has been treated like TTP with plasma exchange therapy. In fact, one of the main arguments against distinction of aHUS from TTP has been that both are treated similarly with plasma exchange. Now, with anticomplement therapy clearly shown to be superior to plasma therapy, a new approach to the diagnosis and management of aHUS is in order and discussed in this review.

MAHA, Thrombotic Microangiopathy, and New Definitions of aHUS and TTP

The syndrome of MAHA and thrombocytopenia is often mistakenly equated with thrombotic microangiopathy (TMA). In fact, MAHA with fragmentation of the red blood cells is a consequence of intravascular mechanical injury. Microangiopathic hemolytic anemia is common in patients with vascular devices such as ventricular assist devices, prosthetic heart valves, or extracorporeal membrane oxygenators. Among patients without a vascular device, at least 5 different types of pathology in the arterioles and capillaries have been associated with the syndrome of MAHA and thrombocytopenia (Table 1). These lesions share the common feature of arteriolar stenosis, which generates abnormal shear stress to cause red blood cell fragmentation. Thrombocytopenia often accompanies MAHA because arteriolar stenosis is due to thrombosis in most cases. In metastatic diseases, thrombocytopenia may result from bone marrow involvement.

TMA is only one of the lesions that are associated with the syndrome of MAHA and thrombocytopenia. On the other hand, TMA does not always present with the syndrome - it is not uncommon to encounter patients with TMA in kidney biopsy performed for renal dysfunction, yet without MAHA or thrombocytopenia in the peripheral blood. This is because MAHA and thrombocytopenia are only apparent when thrombosis and arteriolar stenosis are extensive to cause notable thrombocytopenia and red cell fragmentation. A similar distinction is also seen between TTP and the syndrome of thrombocytopenia and MAHA: most cases of TTP present with thrombocytopenia and MAHA; yet, occasionally a patient of TTP may present with stroke or transient ischemic attack without apparent thrombocytopenia or MAHA [7].

The limitation of the conventional definition of aHUS as a syndrome of MAHA, thrombocytopenia, and renal failure and its overlap with TTP and other causes of MAHA can only be resolved by redefining aHUS and TTP according to their pathogenetic mechanisms (Table 2). The mechanistic definitions, based on the findings of genetic or autoimmune antibodies affecting the regulation of the alternative complement pathway in aHUS and of the proteolysis of von Willebrand factor by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeat, member 13) in TTP [8–10], encompass patients who do not have both MAHA and thrombocytopenia and provide the basis for rational management of both disorders: plasma exchange or future recombinant ADAMTS13 proteins to replenish missing ADAMTS13 and rituximab to suppress ADAMTS13 inhibitors for TTP; and anticomplement therapy to suppress incessant complement activation for aHUS.

TMA is the Consequence of Endothelial Injury

The pathology of TMA comprises 2 components: microangiopathy, presenting as endothelial cell swelling, necrosis or disruption, often accompanied with subendothelial edema or expansion; and thrombosis (Fig 1A-E). It is believed that endothelial injury is the primary event in TMA whereas thrombosis occurs at sites of endothelial cell disruption where platelets and blood coagulation proteins come in contact with exposed subendothelial components. Notably, TMA does not include TTP, which is characterized with VWF-rich arteriolar and capillary thrombosis but, except for microscopically undetectable apoptosis, no apparent evidence of microangiopathy (Fig 1F-H).

The pathology of TMA may result from at least 7 different mechanisms of endothelial injury (Table 1). The best known is shiga toxin–induced endothelial cytotoxicity in the hemolytic uremic syndrome after infection with shiga toxin–producing *Escherichia coli* or other microorganisms. Thrombotic microangiopathy can also occur in patients with pneumococcal sepsis and less commonly other infections in which microbial neuraminidases expose the Thomsen-Friedenreich antigen on endothelial and red cells, subjecting the cells to attack by preexisting antibodies against the antigen [11,12].

Thrombotic microangiopathy can occur with anti–vascular endothelial growth factor (VEGF) drugs such as bevacizumab, a humanized monoclonal antibody of VEGFA [13–16]. Anti-VEGF therapy disrupts the VEGF signaling pathway in glomerular endothelial cells, resulting in glomerular microangiopathy and occasionally thrombosis. Thrombotic microangiopathy is also known to occur in association with a variety of other drugs such as mitomycin, gemcitabine, calcineurin inhibitors, quinine, and cocaine, via as yet unknown mechanisms.

In patients without infections or drugs, 3 groups of molecular defects have been detected. Atypical hemolytic uremic syndrome with mutations causing defective regulation of the alternative complement pathway is the most common and will be the subject of this review.

In TMA of infancy onset, mutations causing loss of function of *diacylglycerol kinase epsilon* (*DGKE*) is detected in approximately 20% of the cases without mutations affecting complement regulation [17]. *DGKE* mutations are also detected in patients with the diagnosis of membranoproliferative glomerulonephropathy (MPGN) [18]. The difference in diagnosis (TMA vs MPGN) depends on whether thrombosis is detected in the kidney biopsy. DGKE nephropathy is different from aHUS because it is often associated with more serious proteinuria and anticomplement therapy does not prevent the relapse of TMA [17].

Thrombotic microangiopathy occurs in patients with mutations of the *methylmalonic aciduria and homocysteinuria type C* (*MMACHC*) gene (ie, cobalamin C disease), presumably due to high plasma levels of homocysteine. Most patients of cobalamin C disease have developmental and other complications. Rarely, cobalamin C disease may present as late-onset TMA or MPGN [19,20].

An association of "aHUS" with pathogenic alterations of the plasminogen gene was suggested in a report [21]. However, the evidence is circumstantial and requires further corroboration. In fact, genetic plasminogen deficiency causes ligneous membranitis but has not been found to increase the risk of thrombosis [22,23].