HEMOLYTIC UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA

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INTRODUCTION

The hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are clinically defined entities that present problems in management because of a lack of rational therapeutic approaches. The medical literature contains abundant descriptions of various clinical manifestations, of possible etiologies and of pathogenetic mechanisms, and finally of an equally confusing spectrum of therapeutic approaches. This paper describes the findings in these syndromes and their variants, summarizes promising recent research data, and assesses current therapeutic avenues.

The literature includes descriptions of patients with HUS and TTP with overlapping features (1,2). The classical profile of HUS, however, is that of an acute disease of young children affecting primarily the kidney (2-7), whereas TTP is a life-threatening catastrophic disease primarily of adults in whom renal involvement is usually not severe but in whom the central nervous system (CNS) manifestations are prominent (8-10). However, HUS is seen in adults (11-18) and TTP occurs in children (10, 19); in addition, recurrent HUS has been reported (7, 20). Separation of the syndromes is made complicated by the association of HUS with pregnancy (16, 17), with use of oral contraceptives (18), with the post-partum period (17, 21, 22), and with reports of a congenital form of HUS or TTP (23, 24). This paper will address the subject via the following approach for each of the two major disorders: (1) pathogenesis and pathology, (2) description of the clinical findings, (3) therapeutic approach. And finally, there will be a discussion of the variants.

HEMOLYTIC UREMIC SYNDROME

Pathogenesis and pathology

The understanding of the pathogenesis of HUS requires integration of information derived from epidemiologic studies from hematologic and immunologic observations and from familial studies. In pediatrics, HUS develops following an initiating event which is usually gastroenteritis or less commonly an upper respiratory infection.

The pediatric literature contains abundant reports of infectious agents associated with HUS. Bacteria (predominantly shigella and salmonella but also E. coli), viral agents (Coxsackie A4 and B4, Echovirus 29, myxovirus, Asian influenza, arbovirus, varicella virus, Ebstein Barr virus), a rickettsia-like organism (a microorganism) have been reported as initiating the illnesses which result in HUS (25-36). Attempts to isolate endotoxins have generally proven futile (37, 38) with the exception of Koster et al. (35). Several instances of compromised hosts becoming afflicted with HUS are documented (e.g., thymic lymphoplasia, Wiskott-Aldrich disorder, acute reticulendotheliosis) (6).

The mechanism by which such an insult produces HUS has been the subject of much discussion but convincing corroborating evidence has not yet been presented. The two major hypotheses are: HUS is primarily a disorder of intravascular coagulation with inadequate fibrinolysis or, alternatively, that HUS results from an immunologic process involving either immune complex deposition or activation of the complement pathway.

The view that HUS results from an alteration in normal hemostasis is derived from the following observations. The characteristic hematologic feature of HUS is microangiopathic hemolytic anemia (MAHA) which occurs as erythrocytes traverse glomerular capillaries which are partly occluded by deposits of fibrin (20). These deposits have occurred as a specific or non-specific consequence of injury to glomerular endothelial cells which in turn have become a nidus for platelet aggregation, thereby activating the coagulation cascade but for unknown reasons not triggering adequate fibrinolysis (see Figure 1). Recently, Remuzzi et al. have proposed that HUS may be an example of prostacyclin (PGI₂) deficiency (39). These authors reasoned that prostacyclin may be the most potent endogenous inhibitor of platelet aggregation; in its absence, therefore, the natural mechanism limiting platelet deposition is missing. However, although PGI₂ may have such properties, it is not yet established whether or not synthesis of PGI₂ occurs in human glomerular endothelial cells. Two adults with HUS (40) prior to plasma exchange had depressed levels of PGI₂; following the procedure, levels were normal. Another report in 1981 described a mother and child in whom a factor thought to be capable of stimulating a component inhibiting platelet aggregation, termed plasma prostacyclin production stimulating factor (PSF), was deficient (41). The 2-year-old child developed HUS and, 5 days after hemodialysis had been initiated, was treated with plasma exchange. Prior to exchange, PSF was deficient; during plasma exchange, it was detectable but afterwards it was again decreased in amount when the child had recovered. These authors, however, failed to prove that the factor, PSF, actually stimulated PGI₂.
production. This report is consistent with the view that PGI₂ or other similar factors may play a role in normal hemostasis by prevention of abnormal platelet aggregation.

Evidence that HUS is an immunologically induced disorder is derived from the following observations. Infectious agents have been associated with the development of the syndrome and appear to trigger the disorder by some mechanism (6). HUS has occurred in compromised hosts (6). Altered immunoglobin levels, specifically reduced IgG, increased IgM and IgA, were reported at the onset of HUS by Kaplan et al. (7). Attempts to isolate circulating immune complexes have yielded conflicting results (35, 42, 43). Most investigators have failed to identify circulating immune complexes. Koster et al. (35) prospectively studied 207 children and 34 adults with shigellosis in Bangladesh. Of these, 9 children developed HUS and of these, 4 of 6 had circulating immune complexes detected by the Raji cell method or the C1q solid-phase assay or both (35). In addition, unlike Kaplan and Koornhof (37), who could not demonstrate endotoxemia by a less sensitive method, these authors found that 4 of 7 had endotoxemia as detected by limulus assay (35). This report strengthened the proposal that the gastrointestinal tract becomes altered via an infection and subsequently endotoxin or another substance noxious to the kidney is released and injures glomerular endothelium.

Studies of the complement system and analyses of renal immunopathology lend further indirect proof that HUS may result from an immunologic insult. Early reports failed to detect any change in C₃ levels (6). However, depressions in C₃ levels have now been reported by several authors (35, 42, 44, 45). C₄ levels have been reported by some to be decreased (35, 43-46) and by others to be normal (42, 47). Decreased CH50 has been reported in 2 publications (43, 46) whereas normal levels have also been found (46). Monnens et al (42) measured serum levels of complement components in 10 children with HUS. Measurements of C4, C3, Factor B, C5, Clq, C3b, and C3c were made at the time of admission in 10 and sequentially in 5. C3 was low in 5 of 10, C4 and Clq were normal except for one low Clq, and C3b and C3c were increased in 8 of 9. These authors suggest that levels of breakdown products may be more sensitive indicators of complement activation regardless of pathway.

Activation of the alternative complement pathway has been proposed because of the presence of C3Nef (47), of the presence of fragments of Factor B (i.e., Ba and Bb) (45) and of the presence of IgM and C3 in the glomeruli of renal biopsies obtained early in the course of pediatric patients. Levels of Factor B have been reported to be normal in one study (42) and depressed in another (45). As of the present time, because of the inconsistency of results, activation of either the classical or the alternative pathway of complement as a major or primary mechanism is still unproven.

The final and perhaps the most persuasive evidence that HUS results from immunologic mechanisms is the similarity between its renal pathology and that of renal allografts that have undergone hyperacute rejection (48).