Platelets and the Hemolytic-Uremic Syndrome*

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ABSTRACT

Clinical studies suggest that the microthrombi characteristically found in hemolytic-uremic syndrome (HUS) may be the consequence of an uncontrolled platelet-endothelial interaction. A defect in prostacyclin production which is corrected by normal plasma may be the fundamental pathogenic mechanism. For this reason, efforts should be made to confirm the recent case reports which suggest that plasma infusion or exchange may be more effective than hemostatic inhibitors in the achievement of clinical remission in HUS.

Introduction

The “Hemolytic-Uremic Syndrome” (HUS) was first presented as a disorder in children characterized by hemolytic anemia, thrombocytopenia, and renal failure. Subsequent reports identified the gastro-intestinal prodrome and described the associated microangiopathic hemolytic anemia. Over the next two decades, reports were published which indicated endemic foci of HUS in Argentina, South Africa, France, and California. These studies and the prodromal gastro-intestinal symptoms suggested an infectious etiology. Viruses have been implicated as the etiologic agent in some cases while the occurrence of HUS during an epidemic of shigellosis indicates that bacterial infection may be the cause in others. However, genetic factors may also play a role. In 1975, Kaplan et al described a pattern of familial HUS with a high mortality rate in which siblings contracted the disease at the same age, although years apart. Three years later, Dolislager and Tune drew attention to their lack of prodromal symptoms which further emphasized genetic rather than infectious determinants. The greater mortality in this “genetic” variant was consistent with the analysis published by Stuart et al which had shown that absence of the gastro-
intestinal prodrome predicted a poor prognosis.

Although HUS occurs most commonly in children, it also occurs in adults, especially in women taking oral contraceptives and in women during the post-partum period. The recent report of fatal HUS in three generations of adults from the same family suggests further that genetic factors may be clinically unexpressed until adult life. Since HUS is no longer thought to be confined to the pediatric age group, differentiation from the closely related disorder, thrombotic thrombocytopenic purpura (TTP) has become more difficult.

**Hemolytic-Uremic Syndrome and Thrombotic Thrombocytopenic Purpura**

Amorosi and Ultmann reviewed 271 cases of TTP in 1966 and proposed a diagnostic pentad of hemolytic anemia, thrombocytopenia, neurologic manifestations, fever and renal involvement. This pentad has obvious similarities to HUS. If one compares HUS with TTP it is clear that the anemia is microangiopathic, and the thrombocytopenia may be severe in both HUS and TTP. The primary distinguishing features are neurological symptoms in TTP and renal failure in HUS. However, even these criteria do not eliminate ambiguity. Neurological symptoms can occur in HUS and renal involvement is part of the diagnostic pentad proposed by Amorosi and Ultmann. Consequently, there are no objective clinical criteria that distinguish these two syndromes.

**Pathology of Hemolytic-Uremic Syndrome and Thrombotic Thrombocytopenic Purpura**

Hemolytic-uremic syndrome is a thrombotic microangiopathy of the kidney. Arterioles and glomerular capillaries are occluded by thrombi, and the subendothelial space is expanded and contains fibrin. By contrast, TTP is a more generalized thrombotic microangiopathy and, in the kidney, the most prominent finding is occlusion of capillaries and afferent arterioles with granular thrombi. The presence of thrombi in the renal lesions of both disorders suggests that hemostatic mechanisms play a significant role in pathogenesis. The experimental studies of Vassalli and his coworkers suggest further that the differences observed in the renal lesions of these two disorders may merely reflect different stages of evolution in a lesion induced by a mechanism common to both. Vassalli et al studied the renal lesions produced in rabbits by the intravenous infusion of liquoid (sodium polyanetholsulfonate), thrombin, or thromboplastin. They observed that coagulants produce a sequence of events that begins with conspicuous platelet thrombi, as seen in TTP, and evolves into proliferative changes usually associated with HUS. This is concordant with the work of Feldman et al which demonstrated that platelets were progressively less evident in the lesions of TTP with the passage of time, and with that of Vitsky et al which stressed the evolutionary character of renal lesions and concluded that renal changes in TTP may be identical to those of HUS. If intravascular platelet aggregate formation is the initial event in HUS, then the study of platelet kinetics may be of particular importance in its pathogenesis.

**Platelets and the Hemolytic-Uremic Syndrome**

Harker and Slichter simultaneously measured platelet and fibrinogen survival times in order to distinguish intravascular coagulation from conditions associated with a selectively shortened platelet survival. They demonstrated that in TTP and HUS the platelet survival was de-
creased but the fibrinogen survival was normal. These findings are consistent with the recent description of "exhausted" platelets in these disorders and the lack of convincing evidence for an associated intravascular coagulation. These data all suggest that increased platelet consumption is the major hemostatic alteration in HUS and TTP.

Following endothelial injury, platelets adhere to exposed collagen, release their contents, and induce platelet aggregate formation at the site of injury. Platelet thromboxane (TxA2), the most potent platelet aggregant, is also formed during this process. In 1976, Moncada et al identified prostacyclin (PGI2), a prostaglandin synthesized by aortic microsomes which inhibits platelet aggregation. They suggested that the extent of platelet aggregate formation at the site of vessel injury may be determined by the balance between TxA2 produced by platelets and PGI2 produced by the blood vessel. If true, then defects or alterations in the elaboration of PGI2 by blood vessels could tip the TxA2-PGI2 balance towards excessive platelet-endothelial interaction and provide the fundamental mechanism explaining the formation of platelet thrombi in HUS.

Remuzzi et al achieved a clinical remission in two patients with HUS utilizing plasma infusion and/or plasmapheresis. Moreover, plasma obtained from these patients lacked the capability found in normal plasma to stimulate prostacyclin production. They suggested that HUS may be due to the deficiency of an unknown plasma factor required for the production of prostacyclin. Although the putative "plasma factor" awaits identification, the observation of Remuzzi and his coworkers underscores the relevance of platelet-endothelial interactions to the pathogenesis of HUS and emphasizes the potential importance of therapeutic measures that are directed towards control of platelet reactivity.

**Therapy of Hemolytic-Uremic Syndrome**

The adequate treatment of acute renal failure must be considered the most fundamental requirement of any therapeutic regimen for HUS and the substantial experience of Gianantonio and his colleagues convincingly demonstrates the primary role of dialysis in the care of patients with this disorder. However, the characteristic thrombotic lesion of HUS suggests that therapeutic agents that interfere with hemostatic mechanisms may also be beneficial. Heparin, thrombolytic agents, and antiplatelet drugs have all been used in this disorder. However, their usefulness has been the subject of some controversy.

Kaplan et al and Vitacco et al did not find heparin useful in the treatment of HUS in children. However, Proesmans and Eeckels reviewed the world literature and concluded that heparin had indeed been beneficial. Subsequently, Kaplan and his associates challenged the analytical methods employed by Proesmans and Eeckels and added further arguments against the use of heparin. Thus, the controversy continues. However, the demonstration that platelet consumption rather than intravascular coagulation is the fundamental defect in HUS would seem to eliminate the prime indication for heparin and suggest that the use of inhibitors of platelet function would be more logical. This conclusion is supported by the reports which indicate that antiplatelet drugs are more effective than heparin in treatment of TTP.

Inhibitors of platelet function have not been used extensively in HUS. Nonetheless, the few reports that have been published indicate that drugs such as dipyridamole and aspirin can correct the thrombocytopenia and lengthen the platelet survival time in this disorder. However, it is not clear whether even these agents provide an improvement over what can be achieved by hemodialysis alone. While heparin and thrombolytic agents are as-
sociated with a substantial risk of bleeding, the use of inhibitors of platelet function may not provide sufficient control over platelet-endothelial interactions to prevent loss of kidney function.35 Again, experience in the treatment of TTP may provide the most effective approach to the treatment of HUS.

Recent reports indicate that exchange transfusion or plasmapheresis may induce remission in TTP after inhibitors of platelet function have failed.6,32 The observation of Remuzzi et al30 suggests that an exchange procedure may be equally effective in HUS. Hopefully, further experience will confirm this tentative conclusion. If the plasma of patients with HUS indeed lack a “factor” necessary for normal PGI₂ production, the infusion of plasma, or an exchange procedure in more severe cases, should correct the TxA₂-PGI₂ imbalance which is assumed to underlie the formation of platelet thrombi in this disorder. Plasma infusion or exchange procedures, if successful, would be unquestionably preferable to the use of hemostatic inhibitors which compensate for one defect by producing another.

References


