Hemolytic Uremic Syndrome/ Thrombotic Thrombocytopenic Purpura in the ICU

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Introduction

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are the extremes of a spectrum of clinical presentations [1] of a rare disease first described in 1924 [2] and 1925 [3] by Moschcowitz. The syndrome has a complex etiology and multiorgan involvement. The one common pathological feature of HUS/TTP, in all forms of presentation of this syndrome, is the pathognomonic thrombotic microvascular lesion (Fig. 1). Although thrombotic microangiopathy might be a better, and more unifying, name [1, 4–6], we will refer to the syndrome as HUS/TTP unless the cited literature is more specific. If untreated, HUS/TTP is a syndrome with a high mortality. Despite the fact that the mortality has decreased from 90% to 10–20% [1, 7–14] some patients with HUS/TTP still need intensive care unit (ICU) admission. The reduction in mortality is partly due to improved supportive therapy, of which renal replacement therapy is the most important [12]. The reason for an ICU admission is to provide adequate treatment of cardio-pulmonary complications and the remaining important causes of death [12]. Neurological complications, which occur mostly in the initial phase of the disease, are also important causes of death [9–12]. Buying time is essential because the disease process can be self-limiting and response to therapy requires time.

Clinical Findings

HUS/TTP is characterized by a pentad: Microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological symptoms, and renal failure. In HUS, renal failure is prominent, and in TTP neurological sequelae are more impressive. Not all features have to be present for the diagnosis. Of all patients with HUS/TTP, 40–60% show the classic pentad of symptoms [13]. Patients with HUS may also have neurological symptoms and patients with TTP can show renal impairment. Involvement of the brain and the kidneys is part of the pentad, but all other organs can also be involved [9]. The presenting symptoms depend on the organ(s) involved and the degree of involvement of the affected organ(s).

Hematological Findings

Anemia can be very severe requiring red cell transfusion. The anemia is due to hemolysis which is reflected by the finding of fragmentocytes, increased reticulocytes,

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increased lactate dehydrogenase, increased bilirubin, and decreased haptoglobin. Coombs' reactions are negative, excluding immune mediated hemolysis. Thrombocytopenia can be severe (platelet count $< 10 \times 10^9$/l), although in some patients with HUS, the platelet count can be almost normal. Leukocytes may be increased and a leukocyte count $> 20 \times 10^9$/l is associated with a poor prognosis [15]. Clotting parameters are normal, but fibrin degradation products may be slightly increased [13, 15]. Serious bleeding is a rare complication although cutaneous bleeding can, of course, be seen in TTP. Complement levels are usually normal with the exception of a decreased C3 in some patients [13, 16]. Lactate dehydrogenase and platelet count are good parameters for disease activity, response to therapy and prognosis [17].

Neurological Symptoms

Somnolence, confusion, seizures, coma, hemiplegia, visual disturbances, cerebral nerve dysfunction, headache, disturbed sensibility and psychiatric disorders can all be seen. The symptoms at presentation can be very impressive and they are sometimes, but not always, reversible [13].

Renal Symptoms

Renal involvement can range from complete anuric renal failure in HUS to normal creatinine in TTP. Hematuria and proteinuria are frequent [13, 15]. Hypertension due to a stimulated renin-angiotensin system can be severe in HUS.

Gastrointestinal Symptoms

Some patients, especially children and the elderly, develop HUS/TTP after a gastroenteritis. They may present with bloody diarrhea. Ischemia of the gut due to the microthrombi can mimic an acute abdomen which makes avoiding unjustified surgery difficult.

Cardiac Symptoms

Due to ischemia and bleeding in the heart, dysrhythmias and pump failure can occur [18, 19]. Almost every rhythm disturbance from asystole to ventricular tachycardia and ventricular fibrillation can be seen [18, 19]. Most patients have a sinus tachycardia not explained by fever and anemia [20]. The rhythm problems are caused by bleeding or ischemia in the conduction system. The pump failure seen in HUS/TTP is mainly determined by diastolic heart failure [21]. Edema and bleeding between the muscle fibers cause a decrease in compliance of the ventricle [20, 21]. This hampers the variation in ventricular filling, the normal reaction of the heart to variations in fluid load and cardiac output demand. When filling pressures are measured with a pulmonary artery catheter and the patient receives a fluid challenge, there appear

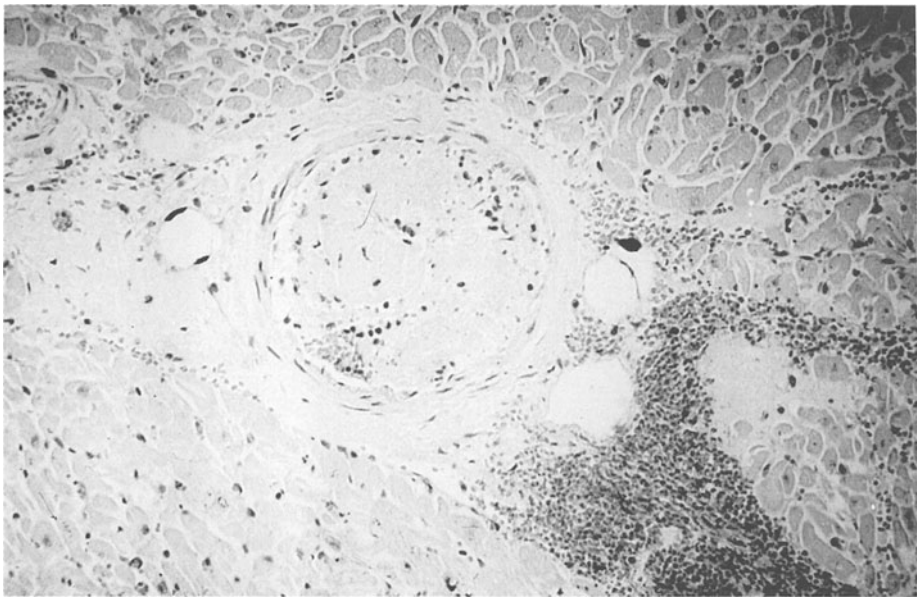

Fig. 1. Microscopy of the heart of a 67-year-old woman with diarrhea associated hemolytic uremic syndrome, who died of cardiorespiratory failure. The microscopy shows an intra-arteriolar thrombus and bleeding between the heart muscle fibers

to be narrow margins between fluid overload and volume depletion. This is also reflected in sinus tachycardia, the remaining compensatory mechanism, seen in most patients. The pump function is further compromised because ischemia and infarction due to microthrombi diminish the contraction power [19]. The histologic features of the cardiac involvement are shown in Figure 1.

Pulmonary Symptoms

Some of the pulmonary symptoms are due to backward failure of the left ventricle causing hydrostatic pulmonary edema. This edema can occur at normal, or slightly increased, pulmonary artery occlusion pressures because the endothelial damage in HUS/TTP causes vascular leakage. The other main cause of respiratory failure is intra-alveolar bleeding. Patients with a transfusion-related acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have also been described. Obviously some of the patients in coma need intubation for airway protection [21–23].

Differential Diagnosis

The most important syndrome that has to be distinguished from HUS/TTP is disseminated intravascular coagulation (DIC). In *de novo* HUS/TTP this distinction can

be made easily. In HUS/TTP there is no consumption of coagulation factors, whereas in DIC this is a main feature. However, when HUS/TTP occurs in patients with an underlying disease, the differentiation can be difficult because diseases like malignancies, human immunodeficiency virus (HIV) and other viral and bacterial infections, and transplantation can also cause endothelial damage and consumption of coagulation factors [24, 25]. Immune hemolytic syndromes are excluded by negative Coombs' tests. Isolated consumption thrombocytopenia, should lead to the diagnosis of idiopathic thrombocytopenic purpura (ITP). Pre-eclampsia/eclampsia can be very difficult to differentiate. Sometimes the reaction to therapy is the only discriminating factor. Although HUS/TTP is a diagnosis based on clinical symptoms, histological findings can support the diagnosis. However the previously advocated gingival biopsy has not shown a high diagnostic yield or specificity [13, 15].

Pathophysiology

The basic lesions in HUS/TTP are thrombi in the small arteries and capillaries consisting mainly of platelets and von Willebrand factor (vWF) and some fibrin. The triggering mechanism in the formation of these thrombi has not yet been determined although several mechanisms have been proposed. Being a syndrome, it might be that there is no single pathophysiological pathway that is responsible, but that HUS/TTP is a final common pathway [14, 26, 27]. The main contributing factors in the formation of thrombi are humoral factors, platelets and endothelial cells. Although plasma of patients with HUS/TTP can induce platelet aggregation *in vitro* [28, 29] and platelet-aggregating factor in plasma and urine is increased, the platelets are believed to play a more passive role [30, 31]. The vWF abnormalities have been the subject of the most extensive study of humoral factors in HUS/TTP. vWF is stored as a multimer in endothelial cells and released at a low rate as smaller conjugates in the circulation. On injury of the endothelial cell, larger conjugates are released into the circulation. These can be detected in the circulation during the various stages of the disease as unusually large vWF. Either alone, or in conjunction with a protease co-factor, unusually large vWF is a strong platelet aggregator [32]. A decreased plasma capacity to process these unusually large vWF has been described in some patients with relapsing HUS/TTP [33]. However the role of vWF is questioned because blocking the von Willebrand receptor on platelets, or the depletion of plasma, does not decrease the platelet-aggregating activity [34]. A second factor supposed to play a role is prostacyclin [35]. In a number of patients, a decreased amount of plasma prostacyclin has been measured. As prostacyclin inhibits platelet aggregation a decrease in prostacyclin could lead to a disequilibrium of platelet aggregators and aggregation inhibitors and hence thrombus formation. Endothelial cells produce less prostacyclin when they are injured [36]. A third humoral factor released by injured endothelium is a platelet aggregating cysteine proteinase which acts as a co-factor for vWF [32] or as a solitary aggregating factor [37].

Most humoral factors are released after injury of endothelial cells. Therefore endothelial cell injury is believed by many to be the first event in the cascade. The endothelium can be damaged by numerous factors and most of them have been mentioned as a possible cause of HUS/TTP. One of the mechanisms described is apopto-

sis, or programed cell death [36, 38]. The complete sequence from signaling upregulation of apoptosis mediators, and the cellular phenotype of apoptotic cells has been described in endothelial cells of organs involved in HUS/TTP. Apoptosis causes a procoagulant state due to decreased prostacyclin production [36]. The identification of the factor binding to the apoptosis receptor is still missing in this sequence.

Verotoxin produced by *E. coli* or *S. dysenteriae* binds to glycolipid receptors (Gb_3, Ga_2 and P_1) and inhibits protein synthesis after internalization [39]. This process is cytotoxic especially in proliferating cells. Verotoxins are only toxic to cells expressing Gb_3 [40]. Toxicity is enhanced by lipopolysaccharide (LPS), tumor necrosis factor (TNF) and interleukin(IL)-1β [26, 40–42] and it is assumed that these molecules induce the synthesis of the verotoxin receptor Gb_3 [43]. The distribution of Gb_3 governs the organ involvement [40, 44]. Binding studies suggest that the receptor in the kidney which binds verotoxin decreases with age, explaining the higher incidence of classic HUS in children [45]. Verotoxin can induce typical HUS and TTP, again suggesting that both diseases are related [39, 46]. Verotoxin also has a direct effect on plasma, generating a platelet-aggregating factor which can not be antagonized by anti-platelet drugs [47].

Several other pathophysiological mechanisms have been nominated as possible primary underlying causes. Lytic anti-endothelial antibodies have been described in the plasma of patients with classic HUS [48] and with classic TTP [29]. Damaged endothelium and partial vessel occlusion increase shear stress which also propagates platelet aggregation, probably by damaging the endothelium further as measured by the release of vWF multimers [4]. In streptococcal and some viral infections neuraminidase can expose antigens on platelets and red cells which are then recognized by agglutinating antibodies [26]. In this type of HUS/TTP endothelial damage is secondary to platelet aggregation. HIV infection, cyclosporin A, tacrolimus, cytostatic drugs, irradiation, solid organ and bone marrow transplantation are thought to damage endothelial cells directly [4, 24, 25, 49].

A congenital cause has been suggested in chronic relapsing TTP and in familial clusters [16, 33, 50, 51]. Genetic defects in several plasma factors playing a role in the equilibrium regulating thrombus formation have been suggested to render patients more prone to HUS/TTP [4, 52, 53].

The hemolysis was thought to be caused by disruption of erythrocytes in partly occluded blood vessels. However receptor mediated processes also play a role [54]. Shear stress disrupts the adherence of red cells to the endothelium by unusually large vWF bridges [4].

Therapy

The treatment of choice is plasma supplementation. This therapy was discovered by serendipity [55]. The fact that some patients recover after plasma infusion alone [7, 56] would suggest that this therapy substitutes for a deficiency in patient plasma. The amount of plasma required is estimated at 40 ml/kg body weight. Most patients, especially oliguric patients and patients with cardiopulmonary involvement, need plasma exchange therapy to meet this requirement [56, 57]. There is no clear dose response relation but in patients not responding to an exchange of 40 ml/kg plasma

daily, exchanges of up to 140 ml/kg have been described as effective [56]. The fact that patients on plasma exchange fare better than patients on plasma infusion, and that patients not responding to plasma infusion can achieve a remission on plasma exchange, suggests that treatment with large quantities of plasma is more effective [8, 52, 56]. Early plasma exchange has been claimed to have beneficial effects on preserving renal function [11] but in the advanced stages this has been questioned [4]. Plasma therapy in typical HUS in children has no proven beneficial effect, probably because the natural course of this disease is benign [4].

There is no proof that fresh frozen plasma is better than cryosupernatant plasma. However in some patients who do not react to fresh plasma, remissions with supernatant plasma have been described. The lack of vWF in supernatant plasma has been thought to be responsible for this finding [56, 58]. The determining factor in plasma remains to be elucidated. Both fresh and supernatant plasma can inhibit the induction of apoptosis in endothelial cell [38]. Cryosupernatant plasma contains a factor regulating the accumulation of unusually large vWF [59]. Normal plasma has been suggested to contain an inhibitor of a platelet aggregating factor present in the plasma of some TTP patients [31]. Immunoglobulin G in adult plasma has been suggested to inhibit the platelet-aggregating factor in TTP plasma [60]. In some cases immunoglobulin has been used as rescue therapy but its effect is debated, and deleterious effects have even been described [56, 61, 62].

Plasma exchange can be performed via a two-lumen large bore catheter in either the subclavian or femoral vein. Technically this can be performed simultaneously with dialysis via the same catheter. Bleeding complications are rare despite the thrombocytopenia and uremic thrombocytopathy. One should be aware of possible complications of the infusion of large amounts of citrate.

The effect of therapeutic modalities additional to plasma therapy has been questioned because no differences in illness duration, mortality or long term sequelae have been seen [9]. However, various successful therapies have been claimed. These claims are based on case histories and small open label studies of patients who either do not respond, or relapse on plasma therapy. Some patients with mild symptoms go into remission on steroids alone [7] but this might also have been the case without therapy. Because of this circumstantial evidence most centers include methylprednisolone 1 mg/kg/day in the treatment. Anti-platelet drugs have been reported not to be effective [7] and to increase bleeding tendency [63]. There are no *in vitro* data to support the use of anti-platelet agents. Whether there is a place for anti-platelet therapy when the platelet counts increase, in order to prevent a relapse as proposed by Gordon et al. [64] remains uncertain. Vincristine [65, 66], cyclosporin [67] and prostacyclin [68, 69] have been used successfully in relapsing and non-responding patients. Heparin, initially claimed to be effective in HUS, is of no benefit [9].

Splenectomy is also described as salvage therapy when plasma exchange fails. There is no proof that splenectomy prevents relapse [10, 70, 71]. In desperate cases bilateral nephrectomy has been performed after which progression of disease stopped [72].

When a patient is responding to therapy, the frequency of plasma therapy and the dose of steroids can be tapered. However there is no consensus which schedule should be followed. On relapse, therapy has to be re-instituted and should sometimes be intensified. Overall early and late relapse rates are 7–64% [9, 53, 73].

Supportive Therapy

Although thrombocytopenia may be very severe, transfusion of platelets only worsens the clinical course and should be avoided [64, 74]. Renal failure can be treated with any form of renal replacement therapy. In children 10–20% develop chronic renal failure, in adults this percentage is much higher [15]. Treatment of cardiac complications is very challenging. Electrolyte and acid-base abnormalities caused by the renal failure, which can trigger arrhythmias should be corrected. Cardiac dysrhythmias have to be treated depending on their type. Pump failure requires careful observation of fluid balance. The invasive measurement of filling pressures may be necessary to estimate the optimal fluid load and the requirement for inotropes and afterload reduction. Pump failure should never be a reason for tapering therapy because it is caused by disease activity and not by therapy. It may be a reason to replace plasma infusion by exchange.

The treatment of choice for severe hypertension [11] is angiotensin-converting enzyme inhibition [26]. Gastro-enteritis with *E. coli* O157:H7 needs no treatment [46]. There are suggestions that treatment with antibiotics and/or motility inhibitors can be detrimental [4].

HUS/TTP Classification

Based on etiology, clinical symptoms, course and response to treatment Drummond [75] and Remuzzi [1] proposed a classification scheme. Better definition of the patient population will probably increase insight into the pathophysiologic mechanisms and improve the evaluation of therapies. With some slight modifications the scheme can be viewed as follows:

1) HUS/TTP with a diarrheal prodrome. This type is seen mostly in children and the elderly and can occur as an epidemic. Verotoxin producing bacteria are the etiologic factor. The clinical picture resembles classic HUS most of the time.
2) Hereditary and recurrent HUS/TTP. This form can follow a relapsing pattern. The genetic causes remain to be elucidated, but are probably multiple.
3) Post-infectious HUS/TTP. This form occurs after a clinically obvious infection with a/o. streptococci, non-verotoxin producing *E. coli*, *H. influenzae*, or viruses. Neuraminidase may have a pathophysiologic role.
4) HUS/TTP accompanying systemic diseases such as systemic lupus erythematosus, scleroderma, malignant hypertension and radiation.
5) HUS/TTP associated with pregnancy, the use of oral contraceptives, cyclosporin A, tacrolimus, or anti-neoplastic drugs.

Conclusion

It has become clear that HUS/TTP is a syndrome with a final common pathway but with multiple pathophysiologic mechanisms leading to this pathway. The heterogeneous patient population has made the study of these mechanisms difficult because abnormalities in one patient may not be found in another patient. The evaluation of

therapy is also difficult because of the heterogeneity. However, the benefit of plasma therapy is without much debate and probably the 'earlier the better' and the 'more the better'. The evidence for the use of steroids is circumstantial, but they are incorporated in most treatment schedules. The use of splenectomy, anti-platelet drugs, immunoglobulin, vincristine, prostacyclin, cyclosporin and bilateral nephrectomy is based on case histories and uncontrolled studies and should only be used as salvage therapy or in relapsing patients. ICU admission is justified because cardio-pulmonary complications, which can be treated well in the ICU, are major determinants in outcome.

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