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Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: Diagnosis and treatment

■ ABSTRACT

Prompt recognition of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) and initiation of plasma exchange treatment is critical as it substantially decreases mortality. Nevertheless, death and long-term complications remain common. The recent relaxation of diagnostic criteria has dramatically increased the number of patients treated for clinically suspected TTP-HUS.

■ KEY POINTS

TTP and HUS are now generally considered a single syndrome, since they are clinically and pathologically indistinguishable.

The diagnosis of TTP-HUS is not precise. In some patients with clinically suspected TTP-HUS, an alternative cause for the signs and symptoms will become apparent.

Plasma exchange is the principal treatment for TTP-HUS; other treatments are unproven.

Major complications from plasma exchange treatment, related both to the central venous catheter and to plasma transfusion reactions, are a common cause of morbidity and an occasional cause of death.

Following recovery from TTP-HUS, long-term risks include the potential for relapse and chronic renal failure.

THE ABILITY OF PLASMA exchange to reduce illness and death from thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) has increased the urgency for prompt diagnosis.

Clinicians once considered a diagnosis of TTP-HUS only if patients had all five key clinical features[1]:
- Thrombocytopenia
- Hemolytic anemia
- Neurologic abnormalities
- Renal abnormalities
- Fever.

Today, however, we rarely wait to see if a patient develops the full pentad of symptoms: thrombocytopenia and microangiopathic hemolytic anemia without a clinically apparent alternative explanation are sufficient to establish the diagnosis of TTP-HUS and begin treatment.[2–4] The decreased stringency of diagnostic criteria has dramatically increased the number of patients treated for clinically suspected TTP-HUS.[5]

In this article, we briefly review the pathogenetic features important for understanding TTP-HUS and why they are now considered a single syndrome, then focus on evaluation and management.

■ DEFINING TTP-HUS

Based on recent and remarkable advances in our understanding of its pathogenesis,[6–9] TTP-HUS is best described as a single syndrome, since TTP and HUS cannot be distinguished either clinically or pathologically,[10] and evaluation and management of all adult patients is

TABLE 1

Diagnosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS)*

Primary diagnostic criteria
Thrombocytopenia
  Most patients have platelet counts < 30,000/mL
Microangiopathic hemolytic anemia, defined by:
  Evidence of accelerated red blood cell production and destruction
  Red blood cell fragmentation
  Negative direct antiglobulin test
No clinically apparent alternative explanation for thrombocytopenia and anemia

Other clinical features that support the diagnosis
Renal function abnormalities
  Proteinuria and hematuria common
  Acute renal failure and oliguria less common
Neurologic abnormalities
  Mental status changes common
  Seizures and focal abnormalities less common
Abdominal symptoms
  Pain, nausea, vomiting, diarrhea common

Rare clinical features that suggest an alternative diagnosis
High temperature with chills
  Suggests infection and is evidence against the diagnosis of TTP-HUS
Extensive purpura
  Extensive purpura and digital ischemia are rare and suggest infection

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*The primary criteria are sufficient to establish a presumptive diagnosis of TTP-HUS and begin plasma exchange treatment.[2–4] The additional clinical features support the diagnosis but may not be present. The most important criterion is the absence of an alternative explanation for these signs and symptoms. Abdominal symptoms are present in many more patients than those with infectious bloody diarrhea. Although fever has been regarded as a classic diagnostic feature of TTP-HUS,[1] high temperature with shaking chills strongly suggests infection.

TTP and HUS are treated as the same condition

the same. Although it has been suggested that TTP and HUS are distinct syndromes[11] and that patients with HUS usually do not respond to plasma exchange treatment,[12] current practice is guided by clinical studies demonstrating that the presence or absence of acute renal failure is not related to the severity of thrombocytopenia and hemolysis, to the frequency of neurologic abnormalities, or to the response to plasma exchange treatment.[2,13]

■ **PATHOGENESIS**

Systemic vascular endothelial cell damage appears to be a central phenomenon in the pathogenesis of TTP-HUS. This is supported by evidence of apoptosis of microvascular endothelial cells in spleens removed from patients with TTP,[14] and by evidence that plasma from patients with TTP can cause apoptosis of microvascular endothelial cells.[15]

Endothelial damage may cause the release of von Willebrand factor multimers that are larger than those found in normal plasma.[16] A plasma protease cleaves and decreases the size of these large multimers to their normal size. A deficiency of this protease has been reported in patients with TTP.[11,17] This deficiency may not be specific for TTP, however. Patients with disseminated malignancy may have unusually large von Willebrand factor multimers and deficient von Willebrand factor-cleaving protease activity but no signs of TTP-HUS.[18] Furthermore, a deficiency of this protease may not be sufficient to cause TTP-HUS: patients with congenital protease deficiency may be completely normal, or may only

TABLE 2

Categories of clinical presentations in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS)*

Pregnancy/postpartum
May be difficult or impossible to distinguish from preeclampsia and the HELLP
(HELLP = hemolysis, elevated liver function tests, low platelet count) syndrome

Drug-associated
Allergic
   Quinine, ticlopidine, clopidogrel
Dose-related toxicity
   Mitomycin C, cyclosporine, pentostatin, gemcitabine

Bloody diarrhea
Escherichia coli serotype O:157 and related Shiga toxin-producing enterohemorrhagic bacteria

Autoimmune disorders
Systemic lupus erythematosus
Scleroderma
Antiphospholipid antibody syndrome
Polyarteritis nodosa

Allogeneic bone marrow transplantation
Most patients ultimately diagnosed with sepsis, acute graft-vs-host disease, or both

Idiopathic
No apparent cause or associated condition

Alternative diagnosis
Not apparent or recognized at the time of initial diagnosis of TTP-HUS
   Sepsis
   Human immunodeficiency virus infection
   Disseminated malignancy
   Malignant hypertension

*These categories describe distinct presentations of patients with clinically suspected TTP-HUS and may be important for predicting the duration of required plasma exchange treatment and the risk for relapse. Patients with coexisting autoimmune disorders or with recent allogeneic bone marrow transplantation may not have TTP-HUS, but the severity of signs and symptoms may suggest consideration of plasma exchange treatment for possible TTP-HUS. In all patients with clinically suspected TTP-HUS, physicians must remain alert for an unsuspected alternative diagnosis.

Renal and neurologic signs are no longer needed to diagnose TTP-HUS

have an acute episode of TTP-HUS in association with a risk factor such as pregnancy.[11]

■ DIAGNOSIS OF TTP-HUS

Current diagnostic criteria and other supporting clinical features are presented in TABLE 1. Although renal and neurologic abnormalities are no longer required for the diagnosis of TTP-HUS, they are very common. Most patients have hematuria and proteinuria, as well as mental status changes.

■ DIAGNOSTIC CLUES IN TTP-HUS: RANGE OF CLINICAL PRESENTATIONS

Although all patients with clinically suspected TTP-HUS share the diagnostic criteria presented in TABLE 1, the syndrome is associated with several categories of clinical presentations (TABLE 2). These categories may be important to predict clinical outcomes.

Pregnancy or postpartum status
Large, published case series of patients with

TTP-HUS consistently report that 70% of patients are women and that 10% to 25% of women present during pregnancy or early postpartum.[3,4,19–21] These observations have important implications for diagnosis, management, and prognosis.

Preeclampsia and HELLP syndrome can mimic TTP-HUS. TTP-HUS is often suspected in women with a complicated pregnancy with features of preeclampsia or HELLP (hemolysis, elevated liver function tests, low platelet count) syndrome. In some women, these pregnancy-related syndromes are indistinguishable from TTP-HUS: preeclampsia and HELLP syndrome, in addition to their defining criteria of hypertension and liver function abnormalities, can also be associated with thrombocytopenia, microangiopathic hemolytic anemia, and neurologic abnormalities such as visual scotomata and even seizures.

What happens after delivery: Distinguishing TTP-HUS from preeclampsia and HELLP. Urgent delivery is the most important treatment for preeclampsia and HELLP syndrome. What happens after delivery helps distinguish patients with pregnancy-related syndromes from those with TTP-HUS. If symptoms resolve within several days, then plasma exchange treatment is not indicated. In some patients with preeclampsia or HELLP syndrome, however, profound thrombocytopenia and hemolysis may first appear after delivery, causing suspicion of TTP-HUS and consideration of plasma exchange.

If the patient's condition is not critical, observation for several days after delivery is appropriate. However, if severe mental status changes or other neurologic signs or anuric acute renal failure are present, in addition to severe thrombocytopenia and microangiopathic hemolysis, then prompt plasma exchange treatment is appropriate.

Although some reports suggest that TTP-HUS most often occurs early during pregnancy, in contrast to preeclampsia and HELLP syndrome, which occur later in pregnancy, most reports describe that TTP-HUS occurs in the peripartum phase of pregnancy. This may be because the symptoms and signs of severe preeclampsia and HELLP syndrome can be indistinguishaable from TTP-HUS, and therefore TTP-HUS may be overdiagnosed in peripartum patients.

Does pregnancy trigger TTP-HUS? The concept that pregnancy triggers TTP-HUS is supported by multiple observations in sisters with familial TTP-HUS who had their first episode during their first pregnancy. These observations cause concern about appropriate recommendations for women who have recovered from TTP-HUS and are considering future pregnancies. Preliminary data suggest that most women will have uncomplicated pregnancies and healthy babies.[22] However, the risk for recurrence during a subsequent pregnancy may be high in women whose initial episode did not occur during pregnancy (and therefore, whose initial diagnosis of TTP-HUS was more certain), and especially in women who have had multiple episodes of TTP-HUS.

Drug-associated TTP-HUS

Drug-associated TTP-HUS may represent either an allergic or a dose-related toxic reaction. TTP-HUS due to an allergic reaction is most commonly seen with quinine,[23] although cases have been reported with ticlopidine (Ticlid) and clopidogrel (Plavix) use.[24,25] TTP-HUS due to drug toxicity is seen most often with the antineoplastic drug mitomycin C (Mutamycin).

Quinine. In patients with TTP-HUS due to quinine allergy, acute renal failure is prominent—so prominent that some reports describe patients as having "quinine-associated HUS." As a result, some reports of the causes of "drug-associated TTP" may not include quinine. This confusion can be dangerous if it leads clinicians not to consider quinine as a potential cause when hematologic and neurologic abnormalities dominate the initial clinical presentation of TTP-HUS. The presence of a very high serum creatinine value with a very short history may suggest preexisting renal failure. However, the increase of serum creatinine may greatly exceed the anticipated 0.5 to 1.0 mg/dL/day in patients who have diffuse tissue ischemia.

Plasma exchange treatment is appropriate. The hematologic and neurologic response to plasma exchange treatment is typically (though not always) prompt in TTP-HUS associated with quinine hypersensitivity, but persistent renal failure is common. Recognition of qui-

Postpartum thrombocyto-penia and hemolysis raise suspicion of TTP-HUS

nine hypersensitivity TTP-HUS is critically important to prevent recurrence, since quinine is a common treatment for leg cramps and is readily available without prescription in health products and beverages.[26] The quinine content of these health products and beverages is sufficient to cause TTP-HUS.

Ticlopidine, clopidogrel. TTP-HUS due to a reaction to ticlopidine or clopidogrel is much less common than with quinine. This may be either because the risk with quinine is greater or simply because quinine use is ubiquitous. Recent reports[24,25] suggest that acute and severe TTP-HUS can occur within 2 to 4 weeks after starting ticlopidine or clopidogrel. In contrast to quinine hypersensitivity, patients in the reports on ticlopidine and clopidogrel have been designated only as having TTP.[24,25] However, the designation TTP-HUS would have been more appropriate, since some of the patients apparently had renal failure.

In some reports of clopidogrel-associated TTP-HUS, the drug association is uncertain because the drug was discontinued several weeks before the onset of TTP-HUS, or because TTP-HUS recurred while the patient was not taking the drug.[25]

The demonstration of antibodies to the von Willebrand factor-cleaving protease in some of these patients[25,27] supports the diagnosis of TTP-HUS but does not strengthen the evidence for a drug-induced etiology. Since these drugs are given to patients with cerebrovascular disease or cardiovascular disease or both, presenting symptoms and signs of TTP-HUS may be initially attributed to these preexisting conditions.

Mitomycin toxicity. TTP-HUS due to drug toxicity is most commonly associated with mitomycin C. TTP-HUS may occur in 10% of patients who have received a cumulative dose of more than 60 mg of mitomycin C.[28] Renal failure is prominent. Plasma exchange treatment may be ineffective. The clinical course is usually determined by the underlying metastatic malignancy.

Infection-related
Bacteria that produce Shiga toxin (eg, *Escherichia coli* serotypes such as O157:H7, and *Shigella* species) can trigger TTP-HUS in about 5% of infected adults and children. These enteric infections are often acquired in a food or waterborne epidemic and typically cause acute bloody diarrhea. Older adults and very young children appear to be at highest risk for developing TTP-HUS from this cause.[29] These patients with TTP-HUS should be reported to the state health department.

In young children, acute renal failure predominates, mortality is low, and plasma exchange treatment is not beneficial. Since the management and clinical course in children are distinct, they are appropriately described simply as having HUS. Children without a prodrome of diarrhea and without an apparent infectious prodrome are often described as having "atypical HUS"; their symptoms, response to treatment, and clinical course are comparable to that in adults. These patients may require plasma exchange treatment and may better be described as having TTP-HUS.

Renal failure is also a prominent feature in many adults with infection-associated TTP-HUS, again causing patients in some reports to be described simply as having HUS. Nevertheless, thrombocytopenia, microangiopathic hemolytic anemia, and neurologic abnormalities can be severe, and in some adult patients no renal failure occurs. Mortality in adults is high and plasma exchange is appropriate.[29] The recognition of this cause is important because these adults, similarly to children with Shiga toxin-associated HUS, appear not to be at risk for relapse.

Other infectious agents such as human immunodeficiency virus have been associated with TTP-HUS, but a causal relationship is uncertain. They are discussed below in the section on alternative diagnoses.

Autoimmune disorders
Just as preeclampsia or HELLP syndrome during pregnancy or soon after delivery can mimic TTP-HUS, so can autoimmune disorders such as systemic lupus erythematosus,[30] catastrophic antiphospholipid antibody syndrome,[31] scleroderma,[10] and polyarteritis nodosa. Although case reports suggest that TTP-HUS occurs more often in patients with autoimmune disorders, and that even the

E coli O157:H7 can trigger TTP-HUS in about 5% of infected patients

pathologic lesions may be indistinguishable,[10] it remains unclear if TTP-HUS is an appropriate diagnosis in these patients.

Since the diagnosis of TTP-HUS is typically considered when the signs and symptoms seem too severe to be caused only by the established autoimmune disorder, these patients are critically ill. Mortality is high. Intensive immunosuppression is the principal therapy. Plasma exchange may provide little additional benefit. These patients have a different response to plasma exchange and a different long-term outcome compared with patients with idiopathic TTP-HUS; both exacerbations when plasma exchange treatment is stopped and relapses are rare.

Allogeneic bone marrow transplantation

Many published series have described TTP-HUS following allogeneic bone marrow transplantation, but these reports are difficult to interpret, as the ranges of reported incidence (2%–76%) and mortality (0–93%) are extreme.[32] Although TTP-HUS may occur in some patients after allogeneic bone marrow transplantation, it is more likely that the clinical features suggesting TTP-HUS are caused by transplant-related complications such as systemic infections or acute graft-vs-host disease.[33]

Therefore, in contrast to the urgent initiation of plasma exchange treatment in patients with clinically suspected idiopathic TTP-HUS, the appropriate management in patients following allogeneic bone marrow transplantation may be to first carefully exclude and empirically treat sepsis and acute graft-vs-host disease.

Idiopathic TTP-HUS

The category of idiopathic TTP-HUS is defined only by excluding all other categories. This category should diminish as more causes of TTP-HUS are revealed, such as the recent descriptions regarding ticlopidine[34] and clopidogrel.[25] Patients with idiopathic TTP-HUS in the Oklahoma Registry may most closely represent patients in previously published case series.[1–3,19–21] They may also be similar to patients recently described as having an autoimmune cause involving the von Willebrand factor-cleaving protease.[11,17] Yet

many patients with idiopathic TTP-HUS have acute renal failure.

■ ALTERNATIVE DIAGNOSES

Since we have no gold standard or defining test for TTP-HUS, we must remain vigilant for other diagnoses that may explain the signs and symptoms.

Sepsis and disseminated malignancy

Sepsis and disseminated malignancy can mimic all clinical features of TTP-HUS, and this may not be initially appreciated. The subsequent clinical course may reveal meningococcemia,[1] beta-streptococcal sepsis, cytomegaloviral sepsis, or Rocky Mountain spotted fever.[4] Bone marrow aspiration may reveal unexpected metastatic carcinoma.[4] In some patients, autopsy reveals an unexpected cause, such as fungal sepsis or disseminated carcinoma.[4]

HIV infection and its complications

HIV infection and its complications may mimic TTP-HUS,[35] but there does not appear to be an etiologic relationship between HIV infection and TTP-HUS. Earlier studies described a possible association between HIV infection and TTP-HUS,[3,36] but only 2 of the 234 patients in the Oklahoma TTP-HUS Registry have been HIV positive.

Malignant hypertension

Malignant hypertension, which is certainly easily recognizable, must be considered as a cause of microangiopathic hemolytic anemia and thrombocytopenia, in addition to neurologic abnormalities and acute renal failure.[37]

Other disorders

Even benign disorders may cause initial suspicion of TTP-HUS. For example, a patient with severe pernicious anemia may have marked thrombocytopenia in addition to anemia. The anemia may initially be described as hemolytic because of the high serum levels of unconjugated bilirubin and lactate dehydrogenase. The initial interpretation of the peripheral blood smear may focus more on poikilocytosis than on macrocytosis, and mental status or focal neurologic abnormalities may be prominent.

> **Remain vigilant for other diagnoses that may explain the signs and symptoms**

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In some patients it may not be possible to distinguish TTP-HUS from another acute but ill-defined multisystem disorder, such as the acute respiratory distress syndrome.[38] In these patients, a trial of plasma exchange treatment may be appropriate.[38]

■ TREATMENT CONSIDERATIONS: WHEN TO USE PLASMA EXCHANGE

Plasma exchange is an empiric but very effective therapy for patients with TTP-HUS. Before plasma exchange treatment was used, 90% of patients with TTP-HUS died.[1] Now, approximately 80% of patients survive.

Plasma exchange requires a large-diameter, dual-lumen central venous catheter, similar to that required for hemodialysis. The patient's blood is withdrawn, the plasma is separated from cells by centrifugation, then the patient's cells are returned with fresh plasma. The instruments used for this procedure are the same as the instruments used for routine donation of blood components.

The decision to start plasma exchange is often the most difficult step. Once treatment is started, however, physicians must still remain alert for alternative diagnoses. The algorithm in FIGURE 1 outlines the ideal course of management contrasted with variations commonly seen in clinical practice.

Gauging the response to treatment

The response to plasma exchange treatment varies, perhaps a reflection of the variety of conditions that cause TTP-HUS. Mental status changes may resolve dramatically, though more severe neurologic abnormalities may not respond to plasma exchange. Thrombocytopenia typically does not resolve until after several days, while anemia may actually continue to worsen for several days. Recovery from renal failure is unpredictable, often slow, and may be incomplete in many patients.

A poor response is not easily defined. Any of the following may be considered a poor response to daily plasma exchange:
• Persistent, severe thrombocytopenia and hemolysis after several days of plasma exchange
• Recurrent acute thrombocytopenia and hemolysis after an initial good response while on once-daily plasma exchange
• The appearance of new neurologic abnormalities while on once-daily plasma exchange.

Treating patients who have a poor response

Increasing the frequency of plasma exchange. Treatment may need to be intensified to twice-daily if the thrombocytopenia does not respond within several days or if the thrombocytopenia initially improves but then worsens while on daily plasma exchange.

Glucocorticoids. Although treatment with glucocorticoids is supported by data suggesting an autoimmune etiology,[17] large series of patients who were not treated with glucocorticoids[2] had the same clinical outcomes as in case series in which glucocorticoids were used in all patients.[20] Nevertheless, since there is a rational basis for the use of glucocorticoids, and since glucocorticoids are commonly used in the treatment of TTP-HUS, their addition to treatment of patients who do not promptly respond to plasma exchange is appropriate.

Other treatments. Many other treatments have been anecdotally recommended for refractory cases, including vincristine, splenectomy, intravenous immunoglobulin, immunosuppressive drugs, and antiplatelet drugs. However, the importance of these anecdotal reports is difficult to interpret in light of the unpredictable clinical course of TTP-HUS.

Duration of treatment

Whether to stop plasma exchange abruptly when the platelet count reaches normal or whether to continue it on an intermittent basis to "consolidate" a remission is an empirical decision. In many patients, the condition will promptly exacerbate when plasma exchange is stopped, as manifested by asymptomatic thrombocytopenia and increased lactate dehydrogenase. This has led to a common practice of tapering the frequency of plasma exchange treatment to avoid exacerbations.

The actual duration of plasma exchange treatment required to achieve a durable remission is extremely variable, from less than a week to many months. Prolonged courses of plasma exchange, with frequent exacerbations when treatment is diminished, are most characteristic of patients with idiopathic TTP-

Exchange of one plasma volume once daily is the principal treatment

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The duration of treatment for TTP-HUS is extremely variable

HUS who have minimal or no renal failure. Persistence and patience with plasma exchange is the most effective practice and results in remission in most patients.

Complications of plasma exchange

Major complications are frequent and are related to the requirement of a central venous catheter and large volumes of plasma.[39] TABLE 3 describes complications observed in 71 consecutive patients treated with plasma exchange for clinically suspected TTP-HUS[39]: complications occurred in 43 (61%) of patients; complications were defined as major in 21 patients (30%) and caused two deaths.[39] No transfusion-transmitted infections were detected.

Unintentional platelet removal. An unappreciated complication of plasma exchange treatment is that, with some apheresis instruments and settings, unintentional platelet pheresis may cause persistent thrombocytopenia when other features of TTP-HUS have resolved, potentially causing inappropriate treatment decisions.[40] This complication should be suspected when all clinical features of TTP-HUS resolve except

persistent, moderate thrombocytopenia. Additional treatment is clearly inappropriate in these patients; correct management is to discontinue plasma exchange.

Alternatives to plasma exchange

Fresh-frozen plasma is equivalent to cryoprecipitate-poor plasma for plasma exchange treatment.[41]

Plasma infusions may be used if plasma exchange treatment is not immediately available, but a randomized controlled trial has clearly demonstrated the greater efficacy of plasma exchange.[2]

Platelet transfusion. Although dramatic anecdotes have described sudden deterioration of patients following platelet transfusion, and postmortem observations have suggested that platelet aggregates were the cause of death,[42] these reports may have been merely describing the coincidence of platelet transfusion with acute complications and death. Preliminary data suggest that many patients with TTP-HUS actually receive platelet transfusions, typically before the diagnosis is suspected and plasma exchange treatment is begun, and adverse outcomes are rare.[43]

Platelet transfusions are not required for asymptomatic thrombocytopenia, may not be necessary for procedures such as central venous catheter insertion,[39] but should not be withheld when major bleeding occurs.

■ LONG-TERM CLINICAL OUTCOMES

Most acute exacerbations of continuing, active TTP-HUS occur within 2 weeks of stopping or tapering plasma exchange treatment. Therefore, signs and symptoms of TTP-HUS occurring after more than 30 days of complete remission on no plasma exchange treatment are appropriately termed a relapse and define a new episode of TTP-HUS.

The mortality associated with TTP-HUS recurrence is low for two reasons:
• The patient, by definition, responded completely to plasma exchange previously
• Delay in diagnosis and treatment is unlikely when a relapse occurs.

The risk for relapse is related to the clinical category of TTP-HUS. Relapses are rare in patients who present during pregnancy or after delivery or who have an autoimmune disorder, suggesting a distinction from idiopathic TTP-HUS. In patients with drug-associated TTP-HUS, relapses occur only when the drug is taken again and may not occur at all in patients with enteric infection-associated TTP-HUS who present with bloody diarrhea. On the other hand, in patients with idiopathic TTP-HUS who have no renal failure, the relapse rate may be as high as 30%.

Chronic renal failure may occur in 25% of patients who have renal failure as a component of their initial TTP-HUS. An undocumented but potentially troublesome long-term outcome is the observation that many patients report minor but persistent and troublesome fatigue and problems with memory and concentration. We do not yet know whether these symptoms indicate subtle neurologic abnormalities following recovery from TTP-HUS, comparable to neurocognitive deficits following coronary artery bypass surgery.[44]

Incidental observation of asymptomatic thrombocytopenia

A problem during follow-up is the incidental observation of asymptomatic thrombocytope-nia. Without knowledge of the patient's history, TTP-HUS would never be suspected, yet asymptomatic thrombocytopenia may be the first sign of acute relapse. In some patients, thrombocytopenia or intermittent symptoms have occurred for months prior to the initial diagnosis.[45]

These observations challenge the common opinion that TTP-HUS, in contrast to idiopathic thrombocytopenic purpura (ITP), is either fully active or in complete remission. The critical issue is when plasma exchange should be initiated, a decision requiring careful observation and judgment because of the high risks associated with central venous catheter insertion and plasma exchange.[39]

■ THE OKLAHOMA REGISTRY

Oklahoma has a unique opportunity to describe the clinical features of TTP-HUS because all patients from central-western Oklahoma with clinically suspected TTP-HUS are treated with plasma exchange by a single provider, the Oklahoma Blood Institute. The registry began January 1, 1989. During the 12 years ending December 31, 2000, 234 patients were seen.

The Oklahoma TTP-HUS Registry is not a case series of patients with TTP-HUS, but rather of patients referred for plasma exchange treatment for clinically suspected TTP-HUS. This distinction is critical. Many patients had additional diagnoses when treatment was begun, or alternative diagnoses were subsequently discovered. Some patients in this registry would not be considered to have TTP-HUS when assessed retrospectively but in the opinion of the treating hematologists, TTP-HUS represented the most likely diagnosis at the time of acute presentation, and plasma exchange was considered to be an essential treatment.

Based on 12 years of data, the number of patients treated each year increased from 4 in 1989 to 27 in 2000, consistent with the sevenfold increase between 1981 and 1997 reported from Canada.[5] This remarkable increase may be attributed to increased awareness of TTP-HUS created in our community by the existence of the registry. It clearly also reflects the

Unintentional platelet removal is an under-appreciated complication

decreased diagnostic stringency for TTP-HUS with the inclusion of a broader spectrum of disorders.[4]

The heterogeneity of this registry reflects the clinical reality of evaluation of patients with an acute illness in whom the diagnosis of TTP-HUS is considered. The heterogeneity of the patients in the Oklahoma TTP-HUS Registry, as opposed to patients reported in many case series, emphasizes the inherent difficulties of evaluation and management of patients with acute, multisystem disorders. The data provided from the registry may be described as "medicine-based evidence,"[46] in contrast to data derived from clinical trials with strict inclusion and exclusion criteria which provide us with evidence-based medicine.

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