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Thrombotic microangiopathies

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ABSTRACT

Objective: To review the clinical features and pathophysiologic mechanisms of the thrombotic microangiopathies (TMAs) including acquired and congenital thrombotic thrombocytopenic purpura (TTP), Shiga toxin-induced and atypical (non-Shiga toxin-induced) hemolytic uremic syndrome (HUS), and the TMAs associated with pregnancy, drugs, and organ transplantation.
Methods: PubMed Medline was used to identify articles published from 2000 to July 2013 using the following key words: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, Shiga toxin, ADAMTS13, and eculizumab. Articles in languages other than English, papers available in abstract form only, and nearly all single case reports were excluded. Small series, reports from registries and study groups, reviews, guidelines, and articles concerning pathophysiology and therapy were preferentially considered.
Results: Impaired post-secretion processing of unusually large von Willebrand multimers due to deficiency of ADAMTS13 (IgG antibodies or congenital), dysregulation of the alternative complement pathway (mutations and/or specific antibodies), and endothelial injury are pathophysiologic mechanisms involved in the TMAs. Acquired and congenital TTP are due primarily to severe ADAMTS13 deficiency, atypical HUS is commonly associated with complement dysregulation, and Shiga toxin, drugs, immune complexes, and others likely damage endothelium. However, there is considerable mechanistic overlap, and the TMAs often have multifactorial causation. Plasma procedures, complement pathway inhibition, immunosuppression, and general supportive care are the principal therapies.
Conclusions: The TMAs are very important conditions because of their associated organ damage and mortality rates. Prompt recognition and categorization by both clinical presentation and pathophysiologic mechanisms should become routine as they are crucial to an optimal treatment plan. Treatment advances have substantially reduced the morbidity of these disorders. Investigational therapies are promising.

Introduction

The thrombotic microangiopathies (TMAs) comprise a group of distinct disorders affecting mostly children and young to middle-aged adults. The TMAs are exceedingly important because of their associated organ damage and mortality. Owing to their rarity, virtually all clinical information and results of therapies have come from case reports, small series, registries, and reviews, but thanks to careful clinical observations coupled with advances clarifying the multifactorial interplay of triggering factors with autoimmune-mediated and/or genetically aberrant post-secretion von Willebrand factor processing and alternative complement pathway regulation, plus important treatment advances, patients' prospects for organ preservation and survival have improved. The TMAs are herein considered together because clinicians must be familiar with the spectrum of disorders in order to diagnose and treat effectively.

Methods

PubMed Medline was used to identify articles published from 2000 to July 2013 using the following key words: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, Shiga toxin, ADAMTS13, and eculizumab. Articles in languages other than English, papers available in abstract form only, and nearly all single case reports were excluded. Reports from study groups and registries as well as published guidelines were especially considered in this review, including, but not exclusively, the Oklahoma TTP–HUS Registry [1–8], the French Society of Pediatric Nephrology [9], International Registry of Recurrent and Familial HUS/TTP [10], the European Paediatric Study Group for HUS [11], the Renal Association of the British Committee for Standards in Haematology and the British Transplantation Society [12], the Hereditäre Thrombotisch-Thrombozytopenische Purpura und Hereditäres TTP-Register [13], the Clinical Research Center for Rare Diseases [14,15], the German STEC–HUS Registry [16,17], and the French Study Group for aHUS/C3G [18]. The PRISMA guidelines [19] have been consulted and applied to this review.

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Results and discussion

Clinical presentation

When patients with TMAs present for evaluation, hematologic derangements are often the first clue to diagnosis, though findings are non-specific. With mild presentation, modest thrombocytopenia may be the only abnormality, but with increasing severity, Coombs-negative hemolysis with red cell fragmentation occurs with marked thrombocytopenia and organ dysfunction. Serum lactic dehydrogenase of erythrocyte origin is typically elevated, sometimes markedly. Precapillary vascular obstruction by hyaline thrombi composed substantially of platelets and variably fibrin, complement components, and cellular debris is responsible for the end-organ clinical manifestations, morbidity, and mortality [20,21].

The principal target organs are the brain, kidneys, heart, and occasionally lungs and others [21]. In autopsy cases, microvascular thrombi are commonly widespread [22]. Brain involvement may cause headache, altered mentation, agitation, coma, aphasia, hemisensorimotor signs, sudden blindness, and seizures; signs are non-specific, variable, and often waxing–waning [21]. Renal involvement presents as reduced glomerular filtration rate, hypertension, and abnormal urinalysis [21,23]. Cardiac complications are cardiomyopathy, acute ischemic syndromes with troponin elevations, non-specific electrocardiographic abnormalities, bradycardia, tachyarrhythmias, and cardiac arrest that may occur during seizures [24–28]. Pulmonary involvement resembles the adult respiratory distress syndrome [29].

The TMA syndromes

A number of clinical entities have been defined (Table). Describing them will serve as a starting point for later interpolation of pathophysiologic mechanisms and treatment.

Acquired thrombotic thrombocytopenic purpura (TTP). Acquired TTP was the first TMA described by Moschcowitz [20]. It is rare with an annual incidence of 0.2–1 per 100,000 [1]. In its most common, characteristic form, TTP begins abruptly and virulently, occasionally after a febrile, viral-like prodrome; a minor infection [30] or pregnancy [2] may be the trigger. Thrombocytopenia and fragmentation hemolysis are severe, and central neurologic signs exist at presentation or supervene quickly, out of proportion to renal signs. Dialysis-requiring renal failure is rare. Without immediate recognition and intervention, death, often precipitated by seizures and arrhythmias, may come rapidly and suddenly. Before the advent of modern therapy, mortality was about 90% [21].

One-third of TTP survivors experience relapses over the course of years, especially soon after initial presentation [3,31]. Some have persistent cognitive and central neurologic impairments, other chronic health problems, or die prematurely even when TTP is inactive [4,5,27]. About 5–10% of patients later in their course manifest systemic lupus erythematosus [27]. TTP may complicate the course of lupus or other immune-mediated connective tissue disorders, and differentiating TTP from cerebral vasculitis can sometimes be difficult. The occasional association with these conditions and the greater prevalence in females and blacks [1] who are more predisposed to immune-mediated connective tissue disorders have long presciently raised suspicion that TTP might have an autoimmune basis.

Table
The thrombotic microangiopathies (TMAs)

Acquired thrombotic thrombocytopenic purpura (acquired TTP)
Congenital TTP (Upshaw–Schulman syndrome)
Diarrhea-associated (Shiga toxin-induced) hemolytic uremic syndrome (Shiga-HUS)
Atypical hemolytic uremic syndrome (aHUS)
Pregnancy-associated TMAs HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) Preeclampsia Pregnancy as trigger for acquired or congenital TTP, or aHUS
Drug-induced TMAs Thienopyridines (ticlopidine and clopidogrel) Calcineurin inhibitors (cyclosporine and tacrolimus) mTOR inhibitors (sirolimus and everolimus) Antineoplastic agents (mitomycin and gemcitabine) Quinine
TMA after organ transplantation Renal transplantation Lung transplantation Allogeneic hematopoietic stem cell transplantation
Other conditions resembling or causing TMA Infections Severe pulmonary or systemic hypertension Advanced malignancies Disseminated intravascular coagulation

Congenital TTP—Upshaw–Schulman syndrome. This very rare condition with a prevalence of about 0.05–0.4 per 100,000 [13] was well described by Upshaw [32] and is transmitted by autosomal recessive inheritance [13,33,34]. Patients usually experience from childhood recurring thrombocytopenia, fragmentation hemolysis, and organ effects often precipitated by seemingly minor infections or pregnancy [34,35]; patients presenting during adulthood tend to have had milder clinical courses [34]. However, the clinical course in individual patients can be highly variable [13]. An affected sibling or therapeutic response to a plasma-containing blood product may tip off the diagnosis.

Shiga toxin-induced hemolytic uremic syndrome (Shiga-HUS). HUS was first described by Gasser et al. [36]. Enterotoxigenic bacteria, most frequently *Escherichia coli* O157:H7, but also other *E. coli* including O104:H4 that caused epidemic infection in Germany and France in 2011 [37,38], *Shigella dysenteriae*, and *Yersinia* species are causative [39–41]. *E. coli* O157:H7 are gut commensals in cattle. About 50–300 bacteria can establish infection in humans through consumption of contaminated animal or plant materials [42]. About 3–5 days after ingestion, diarrhea develops, often painful and bloody [37,38,43].

About 10–20% of symptomatic infections lead to HUS [37,43]. Shiga-HUS is the commonest TMA, most prevalent in children under the age of 5 years with an annual incidence of 6 per 100,000 [14], although some outbreaks preferentially select adults [37,38]. Severe thrombocytopenia, fragmentation hemolysis, renal failure, and hypertension are characteristic. In extreme cases, the brain and other organs may be involved. The condition is a medical emergency with a short-term mortality of about 5–10% without excellent supportive care. Renal function recovers in 70% to over 90% of cases [12,23,44].

Atypical hemolytic uremic syndrome (aHUS). aHUS is HUS not due to Shiga toxin. aHUS is rare, one-tenth as frequent as Shiga-HUS [14]. First presentations are commonest in children including neonates but may not occur until later in life. About 20% are familial [14], infections may trigger crises [45], and about 10–15% seem to be set off by pregnancy [14]. The end-organ presentation is predominantly renal, but cardiac [46], neurologic [15], and more rarely large artery obstruction [49] may occur. The outlook before recent treatment advances was poorer than for Shiga-HUS, with