Review Article

The history of thrombotic thrombocytopenic purpura research: a narrative review

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Background and Objective: Thrombotic thrombocytopenic purpura (TTP) is a rare but debilitating thrombotic microangiopathy that results from severe deficiency of the enzyme ADAMTS13. The disorder was first described in the early 20th century, but the pathophysiology of the disease has only been elucidated in the past three decades. In this narrative review, we will summarize the milestone moments in the history of TTP research and discovery.

Methods: We searched literature using PubMed from 1924 to 2023 using the following free text searches: "thrombotic thrombocytopenic purpura", "Moschcowitz disease", and "thrombotic microangiopathy". We found 6,917 peer-reviewed articles and sorted through these for relevant literature pertinent to the review. A total of 46 articles were included for review and the remainder were excluded.

Key Content and Findings: The history of TTP research was reviewed, with a sampling of major events in the evolution of the understanding of the pathophysiology and treatment of the disease discussed here. There remains much to be learned about the nature of the disease in order to develop more specific and less harmful treatments.

Conclusions: An overview of the major discoveries that have led to our current understanding of TTP reveals the results of collaboration of multiple groups of physicians and scientists through the past century, with additional breakthroughs likely to occur in the future because of that same collaborative spirit.

Keywords: Thrombotic thrombocytopenic purpura (TTP); thrombotic microangiopathy; therapeutic plasma exchange; von Willebrand factor (VWF)

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Introduction

A 16-year-old girl presented with 1 week of fever, joint pain, and progressive upper extremity weakness to Beth Israel Hospital in New York City in 1924 (1,2). Eli Moschcowitz, a Hungarian-born internist, worked at that hospital at the time and published reports describing her clinical course. The patient was pale with scattered petechiae, with laboratory evaluation consistent with anemia. The patient developed renal failure early on in her clinical course. Her condition worsened. She went into a coma, and soon after died. Autopsy revealed "pale myocardium" and "hyaline" thrombotic occlusion of terminal arterioles and capillaries, consistent with a microvascular thrombotic component to

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Table 1 The literature search strategy summary

Items	Specification
Date of search	October 17th, 2023
Databases and other sources searched	PubMed, ClinicalTrials.gov, personal files of authors
Search terms used	"Thrombotic thrombocytopenic purpura", "Moschcowitz disease", and "thrombotic microangiopathy"
Timeframe	1924–2023
Inclusion and exclusion criteria	Inclusion: peer-reviewed articles
	Exclusion: materials not necessary to convey a brief overview of the history of TTP
Selection process	All authors conducted the selection with independent searches

TTP, thrombotic thrombocytopenic purpura.

the disease that ultimately decided the fate of this child. This was the first case report describing what eventually became known as Moschcowitz disease, which we now know as thrombotic thrombocytopenic purpura (TTP) (3-5).

The history of TTP exemplifies the best application of the scientific method. Hundreds of scientists and physicians, both sung and unsung, have come together through the generations to not only identify and describe this serious and deadly rare disease, but to render it a treatable illness. Any questions worth investing the time and energy to answer require open and curious minds to share their ideas, accept their mistakes, and amplify their successes. Here, we will describe some of the major discoveries in the past 100 years that have led us to our current understanding of the pathophysiology and optimal treatment paradigms for TTP. We present this article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.org/article/view/10.21037/aob-23-46/rc).

Methods

We performed a literature search through PubMed from 1924 to 2023 using free text: "thrombotic thrombocytopenic purpura", "Moschcowitz disease", and "thrombotic microangiopathy" (*Table 1*). We found a total of 6,716, 17, and 4,637 peer-reviewed articles, respectively. Of these, the vast majority did not specifically outline the history of TTP, while we found 46 references sufficient for an introductory discussion of some of the major events related to the history of the disease.

Results

Initial discovery and early reports

For many years after Dr. Moschcowitz first published the case report of the unfortunate 16-year-old girl who died of TTP, there was no definitive treatment for the disease, though some patients did respond to infusions of whole blood and plasma exchange; the latter was first attempted in 1956 by Wile and Sturgeon, but did not become standard of care until many decades later (6). In 1959, Dr. Michael Rubinstein and colleagues at what was known at the time as Cedars of Lebanon Hospital in Los Angeles described the case of an 11-year-old girl (7). The case was almost identical to previously published reports of patients with Moschcowitz disease, which was by this point referred to as either TTP or chronic thrombocytopenic purpura. This child presented with 1 week of fever, nausea, vomiting, hematuria, and progressive stupor and confusion. She was pale with petechiae on physical exam, and also had laboratory evidence of hemolysis and thrombocytopenia. Her cognitive status progressively declined. With limited to no options as to how to proceed, the physicians caring for the patient decided to try a whole blood exchange transfusion. Remarkably, the patient's symptoms reversed, and she was able to be discharged from the hospital. Clearly, there was something in the blood that was central to the pathophysiology of this disease. The thought at the time was that it was likely that either a plasma-related factor was killing these patients or some important yet heretofore unidentified blood component was missing, since giving

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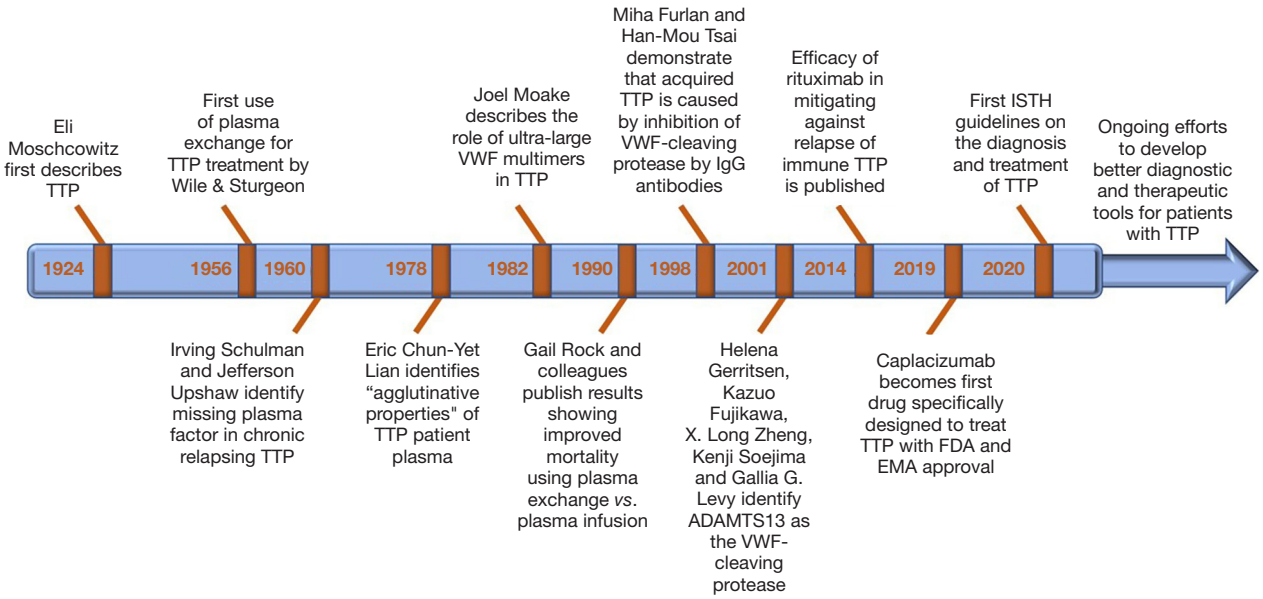

Figure 1 Timeline of selected major events in the history of TTP research. TTP, thrombotic thrombocytopenic purpura; VWF, von Willebrand factor; IgG, immunoglobulin G; FDA, Food and Drug Administration; EMA, European Medicines Agency; ISTH, International Society on Thrombosis and Haemostasis.

exogenous whole blood seemed to help reverse the process (*Figure 1*).

A plasma factor related to disease

A year later in 1960, Schulman *et al.* explained the reasoning behind this hypothesis (8). They described the case of an 8-year-old German boy who had immigrated to the United States in 1954. The boy had chronic thrombocytopenia, and soon after he was under the care of Dr. Schulman and colleagues in Chicago, he underwent a splenectomy as part of a treatment plan for what was presumed to be idiopathic thrombocytopenic purpura, now known as immune thrombocytopenia (ITP). He did have episodes of severe thrombocytopenia in the years he was followed by the group, calling into question the diagnosis of ITP. When he came in with exacerbations, he was repeatedly treated with whole blood transfusions. These interventions would not only help treat his symptoms, but also led to normal or even high platelet counts. However, the effects of the transfusions on platelet counts only lasted for 2–3 weeks, with the platelet count returning to a baseline of approximately 50,000–70,000 platelets per square millimeter. One of Dr. Schulman's colleagues, Mila Pierce, speculated that this was because the plasma from the transfusions took about that long to be cleared from the patient's circulation. Subsequently, they began treating the patient with fresh frozen plasma alone every 3 weeks, with normalization of his platelet counts between transfusions. Analysis of the patient's family members revealed a genetic pattern for the disease. Dr. Schulman's paper is a seminal moment in the history of TTP and those who are curious would be well rewarded to spend time reading his remarkable paper.

In 1978, with plasma treatments for patients not yet the standard of care everywhere, Dr. Upshaw, a hematologist at Baptist Memorial Hospital in Memphis, described his experience over 11 years taking care of a patient with the disease, by now known fairly uniformly as TTP (9). Most of the times that she came in with exacerbations, she had both hemolytic anemia and thrombocytopenia. At first, she was treated for exacerbations with whole blood, with prompt resolution of her symptoms and cytopenias; however, he eventually transitioned to using plasma transfusions to treat the patient, with great clinical responses. At this point, it was fairly clear that these patients had some sort of inherited plasma factor deficiency that caused episodes of microangiopathic hemolytic anemia. To this day, patients who have hereditary, or congenital, TTP, are characterized as having Upshaw-Schulman syndrome in honor of the insightful physicians who have helped us to identify these

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patients and treat them appropriately (10) (*Figure 1*).

Congenital versus acquired TTP

Unfortunately, even by the mid-1970s, over 50 years after the disease was first described, the majority of patients who presented with signs and symptoms consistent with TTP did not do well (11). Treatment with plasma infusions tended to be most helpful for pediatric patients and those with a hereditary disease pattern, but most patients with TTP were adults with no known hereditary associations. The latter group appeared to have a different pathophysiology of the disease, since plasma transfusions were only partially successful, and improvements in thrombocytopenia for many of these patients lasted for only days, at most (5). The majority of these unfortunate patients died within a few days of diagnosis. To help improve the treatment paradigm for this, Dr. Bukowski and colleagues at the Cleveland Clinic decided to try a different approach (12). They speculated that there may be more than one etiology of TTP, and that at least for some patients, there was a "soluble toxic material" involved in the pathophysiology of the disease. In 1976, Dr. Bukowski reported his experience treating TTP over the past 16 years, with whole blood exchange transfusions in 15 such patients and lasting remissions occurring in nine of them (13). Dr. Rock and other physicians in the Canadian Apheresis Study Group published a landmark trial in 1991 canonizing therapeutic plasma exchange as the gold standard for treatment for TTP, which it remains to be for the acquired form of the disease at the time of this publication (14). They reported the superiority of plasma exchange compared to plasma infusion in terms of mortality. Very few medical interventions in the history of humanity have been shown to be as impactful as therapeutic plasma exchange for the treatment of TTP.

On the other hand, the casual reader may be asking, how do you know whom to treat? And once you decide to treat a patient, to whom do you give simple plasma transfusions and who gets plasma exchange? There are obvious logistical and clinical complications that can arise from either treatment modality. Transfusing any human blood product, including fresh frozen plasma, can lead to immune-mediated reactions, up to and including anaphylaxis and death (15). Plasma exchange for TTP requires the placement of an invasive central catheter in patients with severe thrombocytopenia (16). What if these patients do not need the procedure? Are we not potentially causing unnecessary harm for these patients who may have a completely different reason for their microangiopathic hemolytic anemia and thrombocytopenia with completely different treatments required? The race to answer these questions was on. A deeper understanding of the pathophysiology of the disease was needed.

Insights into the disease mechanism

Towards exploring the pathophysiologic mechanisms that cause TTP, Dr. Lian at the University of Miami reported in 1979 that plasma from patients has "agglutinative properties" (17). Something about the plasma of these patients was causing platelets to aggregate in *in vitro* studies. It was in 1982 that Dr. Moake at Boston University was able to tell us why platelets were aggregating in these test tubes (18). He noted that the plasma of patients with chronic relapsing TTP in remission had "ultra-large von Willebrand factor (VWF) multimers" and proposed that patients with the disease had an absent "VWF depolymerase". At long last, the biggest clue as to what was happening to these patients was becoming much clearer. VWF is a large multimeric glycoprotein. We now know, in large part due to the work of Dr. Moake and others, it is a sticky protein that binds to platelets via its A1 domain and helps in the process of primary hemostasis (19). TTP now appeared to be connected to a problem with regulating the size of these multimers of VWF.

As techniques in biochemistry and biology rapidly improved in the 1980s and 1990s, so too would the tools used to help derive further insights into the pathophysiology of many diseases, including TTP. In 1996, the existence of a VWF-cleaving protease (VWF-cp) was identified by Dr. Furlan and colleagues in Bern, as was the cleavage site on VWF in its A2 domain between Tyr1605 and Met1606 (20). These residues corresponded with the VWF peptide bond cleavage site earlier reported in normal plasma and plasma from patients with type IIA von Willebrand disease, a bleeding disorder in which VWF is excessively susceptible to enzymatic degradation (21). In that same year of 1996, Dr. Tsai reported that the effect of VWF-cp was found to be dependent upon shear stress, indicating that when low shear stress is present in the vasculature, VWF remains unaffected by the enzyme (22). Though this finding suggests a role of the conformational environment of VWF on the efficiency of the VWF-cp, both groups confirmed the hypothesis by showing that cleavage of VWF was enhanced in the presence of urea or guanidinium chloride (20,22).

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The basic building blocks were in place by that time to explore what was happening in the plasma of patients with TTP. In 1997, Furlan and colleagues reported the interesting findings associated with four patients with chronic relapsing TTP, including two brothers (23). All four patients had ultra-large VWF multimers and constitutional deficiency of protease activity. Mixing the plasma from the patients with normal plasma at a 1:1 ratio showed no inhibition of VWF-cp in normal plasma. These findings were reminiscent of findings in the patient cared for by Dr. Upshaw, and implied that such patients had a hereditary deficiency of VWF-cp.

In contrast, and by extrapolation, simple infusion of a deficient factor would be sufficient if the main mechanism of disease was VWF-cp deficiency. As the reader is already aware, outcomes were significantly better with plasma exchange than with simple plasma infusion. Insights into the pathophysiology of the disease became clearer in 1998. For context, here we will describe a case reported by the team in Bern of a patient with acute TTP who was closely followed over more than 1 year (24). Severe VWF-cp deficiency was diagnosed at the patient's first bout of TTP. Prolonged plasma exchange, fresh frozen plasma replacement, and steroids were used to treat the patient. The patient was able to enter remission and normalization of VWF-cp. Crucially, identification of an immunoglobulin G (IgG) inhibitor of the VWF-cp was reported in the initial plasma sample. Several months later the patient had another bout of acute TTP with severe VWF-cp deficiency and reappearance of an inhibitor. Once again, treatment led to remission. The patient had a second relapse 330 days after the initial episode, again with severe VWF-cp deficiency. Due to the frequent relapses, splenectomy was performed on day 365, leading to lasting remission and lasting normalization of VWF-cp, as well as lasting disappearance of IgG inhibitor, the first time a VWF-cp inhibitor was described in the literature.

Accumulating evidence was mounting that VWF-cp deficiency was central to the pathophysiology of TTP, and that in the acquired form, IgG inhibitors of VWF-cp were present. Here we acknowledge the insights gained by two groups that looked at larger cohorts of TTP patients to explore this solidifying hypothesis and reported their findings in 1998. Furlan and colleagues obtained plasma samples from 53 patients diagnosed with either TTP or hemolytic uremic syndrome (HUS) and found that none of the HUS patients, but all of the TTP patients, had deficiency of VWF-cp (25). Tsai and Lian, in the same year and published in the same journal on the same day, tested for VWF-cp activity and IgG inhibitor in 39 plasma samples from 37 acquired TTP patients at different points of time during their clinical course (26). Both groups found that VWF-cp was deficient during acute TTP episodes, but not when the patients were in remission nor in the plasma of normal subjects. An inhibitor was detected in the majority of the TTP patients during acute episodes and was identified as IgG in all positive tests by both groups. Crucially, the inhibitor was not detectable when the patients with acquired TTP were in remission from the disease.

At this point, important questions were answered. Some patients with TTP are born with congenital deficiency of VWF-cp. Most, however, had acquired TTP with IgG inhibitors. Therefore, they had an acquired VWF-cp deficiency. These discoveries explained why plasma exchange and plasma replacement are better in acquired TTP, whereas plasma infusion alone is an appropriate treatment for congenital TTP (27).

Discovery of ADAMTS13

One major piece of the puzzle remained. What was the VWF-cp? In 2001, the answer came. The VWF-cp isolated from plasma in 1996 was purified to homogeneity by several groups: Gerritsen *et al.* in Bern, Fujikawa *et al.* in Seattle, Soejima *et al.* in Kumamoto, and Zheng *et al.* in St. Louis (20,22,28-32). In parallel the group of Dr. Ginsburg reported a genome-wide linkage analysis in four pedigrees with hereditary TTP (33). Amino-acid analysis of the purified protease as well as the genetic analysis found the same gene/protein, i.e., ADAMTS13 on chromosome 9q34 (28-30,32,33). Plaimauer *et al.* cloned, expressed and functionally characterized active ADAMTS13 in mammalian cells in 2002 (31). Work by Gerhard Antoine and colleagues published in 2003 showed that recombinant ADAMTS13 could be added to the plasma of patients with congenital TTP to rescue VWF-cp activity (34). We now know, from validated clinical assays, that ADAMTS13 deficiency is necessary, but not sufficient, for TTP, and that recovery of ADAMTS13 activity corresponds to resolution of the disease (27,35) (*Figure 1*).

Modern treatments for TTP

Though this is a large topic which requires its own dedicated focus to fully appreciate, we will briefly summarize the remarkable newer options for TTP

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treatment that have been discovered and developed in recent years. Insights into the pathophysiology of immune-mediated TTP (iTTP) have led to the standard use of immunosuppressive treatments for these patients, including the monoclonal B-cell inhibitor rituximab (27,36-38). In recent years, caplacizumab, a nanobody that targets the A1 domain of VWF to prevent adhesion of platelets and their clumping in the microvasculature, has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of TTP, the first and only TTP-specific treatment approved to date (39-42). Rituximab significantly reduces the rate of relapse for immune TTP patients, while recent literature suggests a mortality benefit for patients who receive caplacizumab (43-45). There are ongoing clinical trials using recombinant ADAMTS13 both for the treatment of congenital as well as immune TTP (NCT02216084 and NCT03922308) (46). The landscape of treatment for TTP is evolving continuously thanks to the knowledge base built over the last century by investigators in the field.

Conclusions

The journey from a 16-year-old girl who died in the 1920s to the discovery of ADAMTS13 and the consequences of its severe hereditary or acquired deficiency has led us to remarkable realizations about blood and how it works. Having reviewed the broad strokes of the history of TTP here, we have only scratched the surface of what we now know about both ADAMTS13 and TTP. Since the discovery of ADAMTS13, it is now much easier to identify and diagnose patients with TTP. Nonetheless, most centers still require send-out testing for ADAMTS13 which can take up to a week to result (35). In the meantime, many patients with high suspicion of having TTP will undergo plasma exchange with all its concomitant potential complications, only to find out that they do not have TTP. However, with increasingly available rapid testing of ADAMTS13 activity, overtreating patients with thrombotic microangiopathy who do not have TTP will decrease over time.

Perspective

The future of TTP diagnosis and treatment was built on its past, and we all owe a debt of gratitude to the open minds that have led us to this point and beyond. With future discoveries leading to further refinement of our understanding of the function of ADAMTS13; the mechanism of disease in both congenital and immune TTP; and the interplay between ADAMTS13, hemostasis, and the immune system, we will improve how we care for TTP patients. We hope to drastically decrease the time to diagnosis at health centers around the world, as well as generate more targeted therapies that are easier to distribute and administer with fewer adverse sociobiological obstacles.

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Footnote

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