Published in final edited form as:

Transfusion. 2013 January ; 53(1): 235–237. doi:10.1111/j.1537-2995.2012.03934.x.

First symptoms in patients with thrombotic thrombocytopenic purpura (TTP): what are they and when do they occur?

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Idiopathic thrombotic thrombocytopenic purpura (TTP) is a rare cause of thrombocytopenia and hemolysis characterized by life-threatening end-organ ischemia due to platelet microthrombi. TTP arises from severe deficiency of ADAMTS13 (< 10% activity). Although neurologic symptoms are considered classical of TTP, they are not present in all patients. Previous studies have described other manifestations in a significant percentage of the patients, related or not to hemolysis and anemia.¹ Therefore, physicians must have a high level of suspicion in order to diagnose TTP. Delay to refer a patient for therapeutic plasma exchange (TPE) is potentially fatal.²

Following Institutional Review Board's approval, we reviewed the records of all adults diagnosed with a first episode of TTP at the University of Alabama at Birmingham (UAB) and the Oklahoma TTP-HUS Registry from January 1, 2007 to June 30, 2010 to answer a specific question: What are the first symptoms of TTP and when do they occur? TTP was defined as thrombocytopenia, microangiopathic hemolytic anemia, and ADAMTS13 activity of < 10% . Patients with underlying conditions such as: pregnancy/postpartum, stem cell transplantation, sepsis, systemic malignancy, autoimmune disease, or a bloody diarrhea prodrome, were excluded, even if their ADAMTS13 activity was <10%.

Thirty-four patients met eligibility criteria (23 from UAB and 11 from the OK Registry). Their mean age was 46 years, and 76% were female. Their laboratory data are shown in Table 1. Table 2 displays the initial symptoms and the number of days until the first TPE. While neurologic complaints were the most common (44%), they varied from mild, such as headache or lightheadedness, to serious, such as seizures and focal deficits. The single most common symptom was abdominal pain (23.5%), with or without nausea/vomiting. Less than 10% of patients reported bleeding secondary to thrombocytopenia. The mean number of days prior to TPE was 12, the median was 5.5, and 62% were treated within 7 days.

Our data confirm that patients with TTP present with a wide range of symptoms, not immediately suspicious for TTP, such as abdominal pain, nausea and vomiting. We postulate that some of these symptoms reflect an underlying disease that may have triggered TTP. Influenza, for example, has been shown to induce antibodies to ADAMTS13 and clinical TTP.³ Moreover, we suggest that abdominal pain, not considered classic of TTP, represents intra-abdominal ischemia, as it has been rarely described.⁴⁻⁶ In the past year, we have seen two patients with ADAMTS13 deficiency that died with massive gastrointestinal ischemia and hemorrhage, confirmed by autopsy.

Unfortunately, the nonspecific nature of signs and symptoms of TTP are likely to hamper a physician's ability to suspect it on clinical grounds alone. Unless a complete blood cell count is ordered and the combination of severe thrombocytopenia and microangiopathic hemolytic anemia is noted, it is concerning that some patients may experience a delay in diagnosis. We did not collect any information on how many clinic or emergency room visits our patients had prior to being diagnosed with TTP. Anecdotally, we know that many patients are seen by several physicians until the constellation of history, laboratory values and consultation with colleagues in hematology or apheresis medicine eventually leads to the correct diagnosis of TTP. Indeed, patients included in this study had one or more of the following diagnoses prior to being referred for TPE: meningitis, arthritis, gastroenteritis, systemic lupus erythematosus, immune thrombocytopenia, stroke, urosepsis, diabetic non-ketotic hyperosmolar acidosis, pernicious anemia, pancreatitis, and antiphospholipid antibody syndrome, confirming our concerns.

Acknowledgments

Mr. Griffin was supported by a Minority Medical Student Award by the American Society of Hematology. Dr. Terrell is partially supported by NIH 1U01HL72283-10S1

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Table 1

Laboratory characteristics of patients with TTP:

Test	Result
Hematocrit (%)	17
Platelet count ($\times 10^9/\text{L}$)	24
Creatinine (mg/dL)	1.6
Lactate dehydrogenase (IU/L)	1225
Blood type	
O positive/negative (% of total)	20 (59)
A positive/negative (% of total)	9 (26)
B positive/negative (% of total)	5 (15)

Table 2

Initial symptoms and time to first therapeutic plasma exchange (TPE):

Patient ID	Initial symptom	Days to TPE
	Neurologic	
1	Altered mental status	1
2	Cognitive deficits, focal neurological signs	1
3	Facial weakness	1
4	Headache	2
5	Altered mental status	3
6	Confusion	4
7	Headache	4
8	Lightheadedness	6
9	Aphasia	7
10	Dysarthria	9
11	Headache	9
12	Weakness, lightheadedness	16
13	Headaches	20
14	Weakness, lightheadedness	21
15	Left side tingling, numbness	32
	Gastrointestinal	
16	Nausea/vomiting	1
17	Abdominal pain	2
18	Abdominal pain	2
19	Abdominal pain	3
20	Abdominal pain	4
21	Abdominal pain	5
22	Abdominal pain	5
23	Abdominal pain	6
24	Nausea/vomiting	7
25	Abdominal cramps, nausea/vomiting	8
	Hematologic	
26	Petechiae	5
27	Ecchymoses	14
28	Ecchymoses	19
	Other systems	
29	Dyspnea	3
30	Chest pain	4
31	Dyspnea	8

Patient ID	Initial symptom	Days to TPE
32	Fatigue	8
33	Claudication	12
34	Fatigue, weakness	132