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CHAPTER 6

Different clinical severity of first episodes and recurrences of thrombotic thrombocytopenic purpura

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Abstract

The clinical course of thrombotic thrombocytopenic purpura (TTP) is characterized by recurrent disease episodes in up to 50% of the cases. The clinical presentation and severity of different TTP episodes have not been systematically compared. Laboratory and clinical information from 51 patients with recurrent disease, stemming from 136 patients with TTP included in the Milan TTP registry (URL: <http://www.ttpdatabase.org>), were used to compare episode fatality, symptoms and disease-related laboratory measurements in different disease episodes. The prevalence of severe neurological symptoms (coma, seizures, and focal neurological defects) was significantly lower in recurrences than in the first episode. Platelet counts and haemoglobin levels at presentation were higher in recurrences than in the first disease episode, and lactate dehydrogenase levels were lower. Also episode fatality tended to be lower in the second and third disease episodes than in the first. Recurrences of TTP are generally milder than first episodes. These differences in severity should be taken into account in clinical research on TTP and in patient management.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disease characterized by acute episodes of thrombocytopenia and microangiopathic hemolytic anemia due to disseminated microvascular thrombosis.¹ The clinical presentation of TTP is variable in terms of type and severity of clinical symptoms.²⁻⁵ Before the introduction of plasma exchange (PEX) for the treatment of acute TTP episodes mortality reached 90%, but decreased to 8-30% following the adoption of PEX.^{3, 6, 7} Patients who survive the first acute episode of the disease may remain asymptomatic for the rest of their life or develop one or more recurrence. It has been estimated that approximately one third of TTP patients recur, with a higher risk of recurrence in those with severe deficiency of the von Willebrand factor cleaving-protease ADAMTS13 during acute episodes^{4, 8, 9} and remission.¹⁰⁻¹² Few data are available on the clinical presentation and severity of recurrences. It is not uncommon in clinical practice to observe that TTP patients, aware of their condition and under close medical monitoring after the first episode, are diagnosed with recurrence before the development of such severe symptoms as coma or other signs of severe neurological involvement. Accordingly, Scully et al. observed that patients from the UK TTP registry needed less PEX procedures to reach remission during recurrences than during the first episode.³ However, the different severity of recurrent TTP episodes has never been the object of a systematic investigation. In addition, it is possible that a number of patients who die from a recurrence are not referred for recurrence to expert clinical centers which are the major source of studies on this disease, biasing the perception of the real severity of recurrent episodes. If confirmed, the

knowledge that recurrences are clinically milder than first disease episodes could be useful for those who design and carry out observational studies or clinical trials in TTP, in order to avoid lumping together patients with first episodes and recurrences. It would also help in clinical practice to better balance the risk of recurrent disease with that of side effects from potentially harmful preventive therapies such as the use of immunosuppressive agents.

Patients and Methods

Patients and definition of clinical categories

Between 1999 and 2009 physicians from Italy and 10 additional countries (Hungary, Serbia, Canada, Germany, Iran, Lebanon, Romania, Russia, Slovenia and Turkey) referred patients who had a suspected diagnosis of TTP to the registry established at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre and provided detailed clinical information and, when available, plasma samples. Information was collected using a standardized clinical questionnaire (available upon request). When necessary to fill gaps of information, clinicians were asked to provide additional clinical documentation and samples. Physicians in Milan (L.A.L. or F.P.) reviewed the cases and confirmed or excluded the diagnosis of TTP. Criteria for TTP diagnosis were the documentation of at least one episode of: (a) thrombocytopenia, (b) microangiopathic haemolytic anemia (c) exclusion of alternative explanations for thrombocytopenia (such as the enterohemorrhagic form of hemolytic uremic syndrome, catastrophic antiphospholipid antibodies syndrome, pre-eclampsia and related syndromes, sepsis, systemic inflammatory response syndrome, disseminated intravascular

coagulation, disseminated malignancy or bone-marrow transplantation associated TTP-like syndrome). Remission was defined as persistence of normal platelet counts and hemoglobin levels for at least 30 days after the most recent acute episode and freedom from new disease symptoms. The study was approved by the Institutional Review Board of the Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico and all patients or their tutors gave informed consent. The first TTP episode was classified as secondary when associated to one or more of the following conditions: (1) pregnancy or post-partum, (2) use of drugs reported to be associated with TTP, (3) additional disease associated with TTP (autoimmune diseases or HIV infection). Patients who did not fit these categories were classified as having idiopathic disease. Presence of symptoms in each TTP episode was defined as prevalence of symptoms at presentation or during the acute phase of the disease before remission or death. Symptoms related to thrombocytopenia included petechiae (purpura), ecchymoses and superficial hematomas. Renal involvement included an increase in the serum level of creatinine (serum levels above the normal reference value of each laboratory) or presence of alterations of urinalysis such as proteinuria or hematuria. Severe neurological symptoms were coma, seizure and focal neurological signs (motor/sensory deficit or aphasia). Less severe symptoms (headache, amaurosis fugax, mild gait alterations) were included in the category “other neurological symptoms”. Cardiovascular involvement included acute myocardial infarction, other acute coronary syndromes, increase in cardiac troponin-T, T wave electrocardiographic alterations and severe hypertension. Gastrointestinal symptoms included abdominal pain, vomiting and diarrhea, whereas jaundice was

excluded from this category owing to the confounding effect of hemolysis. The category “other symptoms” included fatigue, dyspnea and other symptoms not included in the aforementioned categories. PEX procedures for each episode were calculated as the number of 1 volume PEX sessions carried out since diagnosis until remission or death; double volume exchanges were considered equivalent to 2 single volume PEX sessions. According to Vesely et al.,⁴ laboratory data recorded as “at presentation” were the most abnormal findings recorded on the day of diagnosis ± 7 days. To compare data from different laboratories, LDH values were normalized to an upper normal limit of 480 IU/L. The plasmatic activity of ADAMTS13 was measured centrally at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre using collagen binding assay on citrated plasma as previously described.¹² Activity of ADAMTS13 below 10% was considered severely deficient. The normal range for ADAMTS13 activity was 46-160%. Data of all patients are included in a digital registry (URL: www.ttpdatabase.org).

Study design

Figure 1 provides a flow-chart of the study design. To assess the severity of different episodes mortality rates were compared. In addition, each disease episode was compared with the others in patients who had more than one episode. Indicators of disease severity used for comparison were the differences in the prevalence of symptoms, in laboratory values (platelet counts, hemoglobin, LDH, and creatinine), and in the number of PEX procedures carried out in the time span between diagnosis and remission or death. In this matched-pair analysis each individual served as a control for him or herself in different episodes. Patients

referred for only one episode were followed-up for vital status to assess how many of them had died of recurrent disease without notification to the caregiver physician and to our registry, because these events might bias the selection of patients with recurrent disease towards non-fatal, less severe cases. This check was carried out only for patients referred from Italian centres. Information on their vital status and (when applicable) cause of death was searched for by different methods: (a) direct contact of the patient, (b) check against mortality registries, (c) postal follow-up through the vital statistic offices of the city of birth or last residence of the patient.

Statistical analysis

Wilcoxon signed-rank test was used to compare continuous variables in the two disease episodes. Categorical variables were compared by McNemar test. P values <0.05 were considered significant. STATA 11 software was used for the analysis (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP)

Results

After exclusion of patients who did not match the diagnostic criteria and those with insufficient information to establish the diagnosis (n=167), 136 patients with TTP were included in the cohort (number updated at July 2009). The general features of the cohort and clinical information on the first disease episode are in Table 1. Twelve patients died of the disease (9% of all patients), 10 during the first disease episode (7.3% of 136 patients with a first disease episode), 2 during the second episode (3.5% of 57 patients referred for more than one episode).

None of the 33 patients who had 3 or more disease episodes died of the disease. Of the 12 patients who died, 9 had severe deficiency of ADAMTS13 (activity below 10%). Plasma samples for the centralized measurement of ADAMTS13 activity were available for 135 patients (99%): for 36 (27%) patients only acute disease samples were available, for 53 (39%) only remission samples and for 46 (34%) both acute and remission samples. The prevalence of severe ADAMTS13 deficiency was higher in the group of patients with availability of acute disease samples (67%, 55/82) than in those without, whereas it was lower in patients with only remission samples available (36%, 19/53). Among the symptom categories analyzed, cardiovascular symptoms had the lowest prevalence (Table 1): an acute coronary syndrome was diagnosed in only 5 patients, 3 of whom had an acute myocardial infarction. Eight of the 136 patients had an acute renal failure according to the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage renal disease) criteria for the definition of renal failure in critically ill patients.¹³ Two of these 8 patients had severe ADAMTS13 activity, three (one with severe ADAMTS13 deficiency) died of the disease at the first episode and only one, who had relapsing episodes, was included in the paired analysis of disease severity. Of 57 patients who had two or more disease episodes, clinical information on the first two episodes of the disease was available for 51 (90%). Their general features and clinical information pertaining to the two episodes are summarized in Table 2. The general characteristics and the clinical features at first episode in patients with recurrence were not different from those in patients without recurrence (not shown), but a severe deficiency of ADAMTS13 activity was more prevalent

among patients who had recurrences (65%, 37/57) than those without (43%, 29/68). In patients with multiple disease episodes, the prevalence of severe neurological symptoms and fever was lower during the second than the first episode (Table 2). Among disease-related laboratory measurements, platelet counts and hemoglobin levels were higher in the second episode, whereas serum LDH was lower (Table 2). Creatinine levels did not significantly differ between the two episodes. Finally, the number of PEX procedures carried out between diagnosis and hospital discharge was smaller for the second episode. Subgroup analyses were performed in groups of recurrent patients with (n=36) or without (n=15) severe deficiency of ADAMTS13. In the group of patients with severe deficiency of ADAMTS13 statistically significant differences were found for prevalence of severe neurological symptoms, fever, hemoglobin levels, platelet counts, LDH values and number of PEX until remission/death. In the group of patients in whom severe deficiency of ADAMTS13 was not found in the available samples (n=15) significant differences in the two episodes were found for platelet counts, hemoglobin and LDH levels. All statistically significant differences found in subgroup analyses were in the same direction of those observed in the primary analysis. Thirty-three (65%) of the 51 patients included in the paired analysis of disease severity comparing the first and second episode in patients with recurrent disease had at least a third disease episode that developed at a median time of 1.3 years (range: 0.3-8 years) after the second episode. The third episode generally displayed milder clinical and laboratory features in comparison to the first and even to the second episode (Figures 2 and 3). The prevalence of purpura ($p=0.004$, McNemar's test, prevalence at first vs

third episode), of severe ($p=0.001$) and other ($p=0.007$) neurological symptoms, and of fever ($p=0.002$) were lower in the third than in the first episode (Figure 2). Hemoglobin was largely influenced by episode number ($p<0.001$, Wilcoxon signed rank test, levels at first vs third episode) and smaller but statistically significant effects were also observed for platelet number ($p=0.004$) and LDH ($p=0.03$), whereas creatinine levels were not influenced by recurrence ($p=0.85$) (Figure 3). Vital status information were requested for Italian patients reported to have survived the first TTP episode and not known to have had additional disease episodes ($n=52$, 75% of the 69 survivors of the first TTP episode not referred for recurrence) (Figure 1). Vital status information through October 2009 was collected for all 52 patients: by phone calls or e-mail contact with the patients ($n=13$, 25%), through mortality registries ($n=16$, 31%), or from the vital statistic office of the birth or residence city ($n=23$, 44%). Only one of the 52 patients had died, from a cause that was deemed unrelated to TTP (rupture of mechanic aortic valve prosthesis).

Discussion

The results of this study show that TTP recurrences usually have a milder clinical course than first episodes of the disease. Neurological involvement, the degree of anemia and thrombocytopenia, which were previously shown to be predictors of 6-month mortality in TTP patients,¹⁴ were less severe in the second and third disease episodes than in the first. PEX sessions employed during second episodes were significantly less than those of the first, corroborating the other study

findings. The third disease episode displayed even milder clinical course than the first two episodes.

There are several plausible explanations for TTP recurrences to be less severe than first episodes. A first argument is that recurrences are more rapidly diagnosed and treated. Indeed, many recurrences were diagnosed on the occasion of complete blood counts, in the presence of the laboratory features of TTP (microangiopathic hemolytic anemia and thrombocytopenia), but with mild or no clinical manifestations. A low prevalence of neurological symptoms, relatively high platelet counts and low number of PEX needed to achieve remission in TTP recurrences were previously reported by Bohm et al. in a study evaluating the course of ADAMTS13 activity during acute TTP, including 11 patients with relapsing TTP and 14 with a first disease episode.¹⁵ However, only two of the relapsing patients of that study were also evaluated during the first episode rendering a direct comparison impossible. Secondly, patients who tend to experience the most severe episodes have the highest risk of death during the first episode, so that survivors as a group tend to have less severe disease. Thirdly, selection of survivors of recurrence might have occurred; this, however, was ruled out by follow-up. An advantage of our study is that 51 patients with 2 or more TTP episodes could be directly compared during their different episodes. This paired-comparison design minimizes the influence of individual determinants of disease severity, which might arise when different individuals are compared in different episodes. The design of this study also allowed minimizing heterogeneity in the ascertainment of clinical characteristics of different episodes in the same patient, because patients were usually referred to the same centre for

first episode and recurrences. Limitations of this study were missing information on some patients and the small absolute number of patients studied. However, given the rarity of TTP and the difficulties of gathering detailed clinical information on clinical episodes we believe that the number and quality of data available for analysis were sufficient to enable the comparison of disease severity described in the study. The overall prevalence of fatal TTP in the TTP cohort of this study was 9%, with lower mortality in relapsing episodes (unmatched analysis). This proportion of fatal disease is consistent with the rate of mortality reported for other cohorts. However, because ours is a tertiary care centre for TTP patients offering free ADAMTS13 testing and medical assistance and counseling, it is possible that recruitment of our patients is biased towards survivors of TTP episodes. Patients who died during the first episode without being referred to our registry do not affect the findings of this study, which is focused on survivors of the first episode who developed recurrences, but may have attenuated the contrast in severity between first and second events. Instead, we reasoned that deaths for TTP occurring during recurrences, not reported to our registry, might have biased this study towards the recruitment of survivors of TTP recurrence, i. e., a less severe subpopulation of recurrent patients. To exclude the presence of this potential distortion of the results, patients referred for a first TTP episode were followed-up to assess whether or not they had died of the disease without notice to the Hemophilia and Thrombosis Centre. The result of this evaluation showed no evidence of this bias, with the only death that occurred not being causally related to TTP. The knowledge that recurrences are generally milder than first disease episodes should be considered in the design and analysis of observational

studies and clinical trials in TTP. An unbalance in the prevalence of patients with recurrent episodes in groups with a risk factor under evaluation or in two different treatment groups might indeed confound the ascertainment of the effect of an exposure or a treatment on acute disease clinical outcomes. The results of this study also have clinical relevance. Although recurrent episodes of TTP should always be regarded as a potentially fatal condition, the relatively less severe clinical course of recurrences should be taken into account when potentially harmful preventive therapies, like long-term immunosuppression, are being planned in patients considered at risk for TTP recurrence.

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Figures

Figure 1. Study flow-chart.

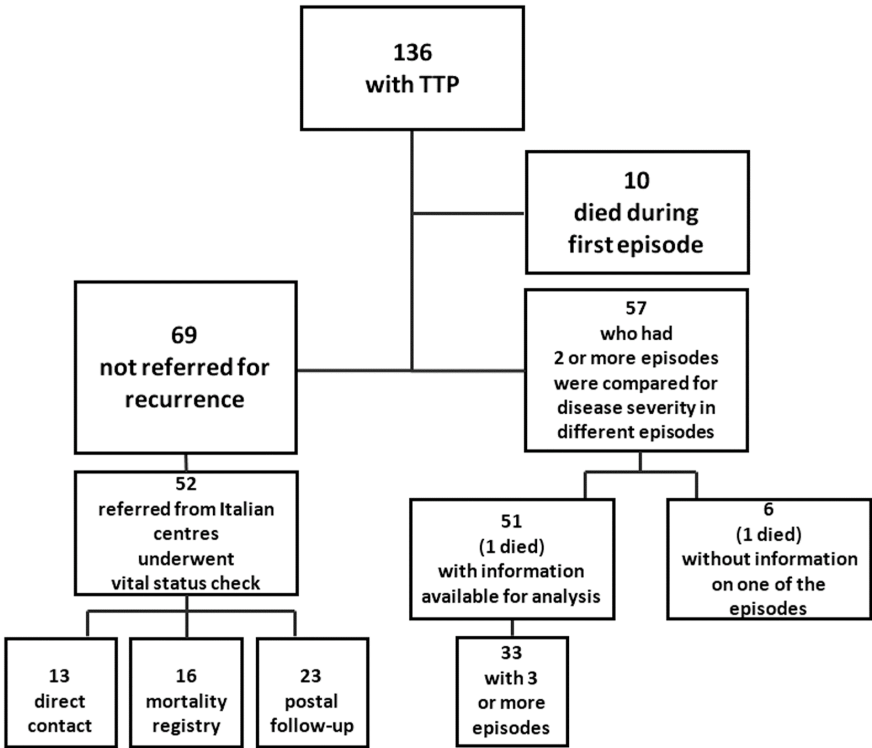


Figure 2. Prevalence of clinical symptoms in different episodes for patients with at least 3 episodes.

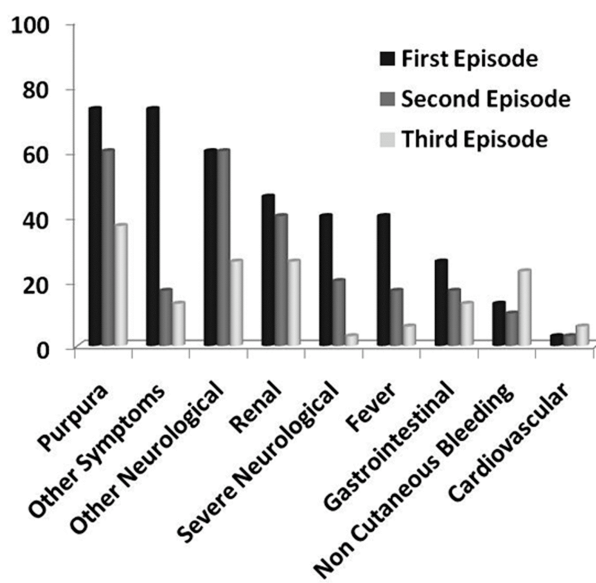
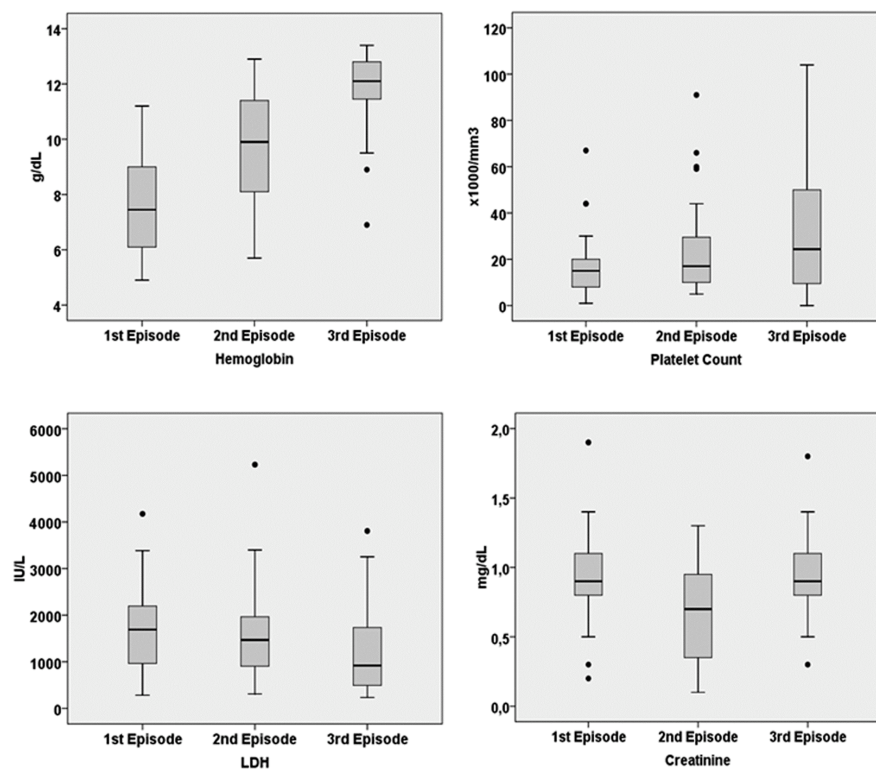


Figure 3. Disease-related laboratory measurements in different episodes for patients with at least 3 episodes.



Tables

Table 1. General, clinical and laboratory features at first episode of the patients included in the study.

Variable	Value
n=	136
GEOGRAPHIC ORIGIN	
<i>Italy</i>	107 (79%)
<i>Other country^a</i>	29 (21%)
REFERRED DURING:	
<i>Acute disease</i>	56 (41%)
<i>Remission</i>	80 (59%)
MALE SEX	29 (21%)
AGE AT FIRST EPISODE, years	37 (28-50)
DIED OF THE DISEASE	12 (9%)
IDIOPATHIC DISEASE	107 (79%)
SECONDARY DISEASE	29 (21%)
<i>Pregnancy</i>	13 (9%)
<i>Autoimmune disease^b</i>	9 (7%)
<i>Drug induced^c</i>	5 (4%)
<i>More than one condition^d</i>	2 (1%)
SEVERE DEFICIENCY OF ADAMTS13 ACTIVITY ^e	74 (54%)
REFERRED FOR MORE THAN ONE EPISODE	57 (42%)
CLINICAL SYMPTOMS AT FIRST EPISODE (n=130)	
<i>Severe neurological</i>	64 (49%)
<i>Other neurological</i>	69 (53%)
<i>Cutaneous manifestations of thrombocytopenia</i>	71 (55%)
<i>Bleeding</i>	15 (12%)
<i>Renal involvement</i>	47 (36%)
<i>Cardiovascular symptoms</i>	15 (12%)
<i>Gastrointestinal symptoms</i>	49 (38%)
<i>Fever</i>	47 (36%)
<i>Other symptoms</i>	50 (38%)
LABORATORY MEASUREMENTS AT FIRST EPISODE (n=117)	
<i>Platelet counts (x10⁹/l)(n=117)</i>	14 (7-22)
<i>Hemoglobin (g/l) (n=117)^f</i>	80 (65-93)
<i>Lactate dehydrogenase (IU/l) (n=113)</i>	1571 (953-2330)
<i>Creatinine (μmol/l) (n=107)</i>	79 (70-106)
TREATMENT AT FIRST EPISODE (n=129)	
<i>Plasma exchange</i>	118 (92%)
<i>Number of plasma exchanges (n=105)</i>	11 (7-19)
<i>Other transfusional therapy</i>	81 (63%)
<i>Immunosuppressive treatment</i>	118 (92%)

Continuous variables were expressed as median (interquartile range).

- Hungary (n=11), Serbia (n=10), Canada, Germany, Iran, Lebanon, Romania, Russia, Slovenia and Turkey (n=1 each).
- Autoimmune thyroid disease (n=5), systemic lupus eritematosus (n=3), myasthenia gravis (n=1).
- Ticlopidine (n=4), clopidogrel (n=1).
- Pregnancy and autoimmune thyroid disease (n=1), pregnancy and systemic lupus eritematosus (n=1).
- Measured during acute disease or during remission.

Table 2. General and clinical features at their first two episodes of the 51 recurrent patients included in paired analysis of disease severity.

Variable	Value	
n=	51	
GEOGRAPHIC ORIGIN		
<i>Italy</i>	41 (80%)	
<i>Other country</i>	10 (20%)	
MALE SEX	11 (21%)	
AGE AT FIRST EPISODE, years	35 (26-44)	
AGE AT SECOND EPISODE, years	38 (30-48)	
TIME TO FIRST RELAPSE	1.7 (0.5-3.7)	
IDIOPATHIC DISEASE	37 (73%)	
SEVERE DEFICIENCY OF ADAMTS13 ACTIVITY ^a	36 (70%)	
REFERRED FOR MORE THAN TWO EPISODES	33 (64%)	
	<i>FIRST EPISODE</i>	<i>SECOND EPISODE</i>
CLINICAL SYMPTOMS (n=51)		
<i>Severe neurological</i>	25 (49%)	9 (18%)
<i>Other neurological</i>	35 (68%)	25 (49%)
<i>Cutaneous manifestations of thrombocytopenia</i>	33 (65%)	29 (56%)
<i>Bleeding</i>	9 (18%)	3 (6%)
<i>Renal involvement</i>	15 (41%)	18 (35%)
<i>Cardiovascular symptoms</i>	2 (4%)	2 (4%)
<i>Gastrointestinal symptoms</i>	18 (35%)	10 (20%)
<i>Fever</i>	21 (41%)	8 (16%)
<i>Other symptoms</i>	17 (33%)	11 (22%)
LABORATORY FEATURES (n=47)		
<i>Platelet counts ($\times 10^9/l$)</i>	15 (8-20)	20 (10-34)
<i>Hemoglobin (g/l)</i>	77 (62-97)	10 (81-117)
<i>Lactate dehydrogenase (IU/l)</i>	1691 (940-2379)	1110 (563-1900)
<i>Creatinine ($\mu\text{mol/l}$)</i>	70 (70-97)	79 (53-114)
NUMBER OF PLASMA EXCHANGES (n=37) ^b	12 (7-19)	7 (5-12)

Continuous variables were expressed as median (interquartile range).

a Measured during acute disease or during remission.

b Information available on n=37 patients for both episodes; information was not available for the first episode in n=6 patients, for the second in n=2 patients, n=6 patients were not treated with PEX.

References

1. Moake JL. Thrombotic microangiopathies. *The New England journal of medicine*. 2002; **347**(8): 589-600.
2. Peyvandi F, Ferrari S, Lavoretano S, Canciani MT, Mannucci PM. von Willebrand factor cleaving protease (ADAMTS-13) and ADAMTS-13 neutralizing autoantibodies in 100 patients with thrombotic thrombocytopenic purpura. *British journal of haematology*. 2004; **127**(4): 433-9.
3. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, et al. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. *British journal of haematology*. 2008; **142**(5): 819-26.
4. Vesely SK, George JN, Lammle B, Studt JD, Alberio L, El-Harake MA, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. 2003; **102**(1): 60-8.
5. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. *Blood*. 2004; **103**(11): 4043-9.
6. Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2010; **115**(8): 1500-11; quiz 662.
7. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *The New England journal of medicine*. 1991; **325**(6): 393-7.
8. Veyradier A, Obert B, Houllier A, Meyer D, Girma JP. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood*. 2001; **98**(6): 1765-72.
9. Kremer Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2010; **115**(8): 1500-11; quiz 662.
10. Ferrari S, Scheiflinger F, Rieger M, Mudde G, Wolf M, Coppo P, et al. Prognostic value of anti-ADAMTS 13 antibody features (Ig isotype, titer, and inhibitory effect) in a cohort of 35 adult French patients undergoing a first episode of thrombotic microangiopathy with undetectable ADAMTS 13 activity. *Blood*. 2007; **109**(7): 2815-22.

11. Jin M, Casper TC, Cataland SR, Kennedy MS, Lin S, Li YJ, et al. Relationship between ADAMTS13 activity in clinical remission and the risk of TTP relapse. *British journal of haematology*. 2008; **141**(5): 651-8.
12. Peyvandi F, Lavoretano S, Palla R, Feys HB, Vanhoorelbeke K, Battaglioli T, et al. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. *Haematologica*. 2008; **93**(2): 232-9.
13. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004; **8**(4): R204-12.
14. Wyllie BF, Garg AX, Macnab J, Rock GA, Clark WF. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. *British journal of haematology*. 2006; **132**(2): 204-9.
15. Bohm M, Betz C, Miesbach W, Krause M, von Auer C, Geiger H, et al. The course of ADAMTS-13 activity and inhibitor titre in the treatment of thrombotic thrombocytopenic purpura with plasma exchange and vincristine. *British journal of haematology*. 2005; **129**(5): 644-52.