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Outcome and relapse risks of thrombotic thrombocytopaenic purpura: an Egyptian experience

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ABSTRACT

Background Thrombotic thrombocytopaenic purpura (TTP) is a rare life-threatening disease. Plasma exchange has significantly decreased the mortality from this disease, which still tends to recur in a substantial proportion of patients. This study describes the clinical spectrum and response to treatment and explores the risks of relapse in a cohort of patients.

Methods Patients treated for TTP at the Clinical Haematology Unit, Cairo University, Egypt, between 2000 and 2008 were identified. Complete demographic, clinical history and full clinical examination, laboratory, treatment modalities and duration, and outcome data were collected and analysed. The follow-up duration was 24 months.

Results 30 patients; 13 men (43%) and 17 women (57%) with a median age of 42 years were treated for 46 episodes of TTP. The median duration of disease onset to diagnosis for the first episode was 7 days. Twenty-three patients (76.66%) were diagnosed as idiopathic primary and seven patients (23.33%) were secondary TTP. Four patients died during the first 24 h. Of the 26 patients, 22 (85.6%) achieved remission with an average of 7.55 plasma exchange sessions, Another nine patients had 25 relapses (mean 2.7). Splenectomy was performed in three patients (11.5%). The 24-month overall survival was 80%. The initial low platelet count and high LDH were the only two statistically significant relapse predictors.

Conclusions The current results conform to the reported literature on the outcome of TTP. The very early mortality due to late referral highlights the need of education about the disease among primary healthcare providers.

Thrombotic thrombocytopaenic purpura (TTP)[1] is a rare but life-threatening disease characterised by microangiopathic haemolytic anaemia and systemic platelet aggregation with consumptive thrombocytopaenia leading to disseminated microvascular thrombosis and fragmentation of erythrocytes resulting in variable signs and symptoms of organ ischaemia and damage.[2–4] Primary TTP arises from congenital or acquired deficiency the enzyme ADAMTS-13, the plasma metalloprotease responsible for regulating the multimeric structure of von Willebrand factor.[5 6] Persistence of the large multimers causes a tendency to increased thrombosis.[7] Secondary TTP accounts for approximately 40% of cases and is more poorly understood. It occurs in the contest of malignancy, haematopoietic stem cell transplantation, pregnancy and with the use of many medications.

The mortality rate of the disease is approximately 95% in untreated cases.[8] The use of therapeutic plasma exchange has reduced mortality rates to 10–20%, with a less favourable prognosis in secondary cases.[9] The disease tends to recur in 20–50% of cases, and combined immunosuppression and even rituximab have been advocated as therapeutic options.[10–12]

In the current study we report on the experience of our tertiary referral centre with 30 patients with diagnosed TTP.

STUDY DESIGN AND METHODS

Our study is a retrospective study that included 30 Egyptian patients treated for TTP at the Clinical Haematology Unit of Cairo University, Egypt, between 2000 and 2008. Ethics committee approval for the study was obtained.

Complete demographic, clinical history, full clinical examination, treatment modalities, duration, and outcome data were collected from the medical records.

Laboratory data included complete blood count, reticulocytic count, blood film for fragmented red blood cells, serum chemistry, lactate dehydrogenase (LDH), Coomb's test. Tests for ADAMTS13 and anti-ADAMTS13 antibodies were assayed for idiopathic patients admitted after September, 2007 using Imubind ADAMTS 13 antigen ELISA ref 813 and Imubind ADAMTS13 autoantibody ELISA ref 814 (American Diagnostica, Stamford, USA).

Patients were followed for a duration of 24 months. Remission was defined as no plasma exchange for 30 days with normalisation of the platelet count and LDH. Refractoriness was reported if symptoms, signs or laboratory changes persisted for more than 30 days following the initiation of plasma exchange, whereas relapse was defined as the recurrence of thrombocytopaenia and microangiopathic anaemia after achieving remission. Disease-related mortality was defined as death occurring during the context of the illness or within 30 days from plasma exchange discontinuation.[13]

Data analysis

Statistical analysis was performed using the statistical package for the social sciences (V.12.0). The results are expressed as median and range. The Mann–Whitney test and the Kruskal–Wallis variance analysis were used to compare group results. Correlation analysis was performed using the Spearman's test.

RESULTS

Thirty patients, 13 men (43%) and 17 women (57%) with a median age of 42 years, were treated for 46 episodes of TTP. The median duration of

disease onset to diagnosis for the first episode was 7 days, with 11 patients (37%) presenting with coma. Table 1 illustrates the clinical data of patients.

Twenty-three patients (76.66%) were diagnosed with idiopathic primary TTP, whereas seven patients (23.33%) were secondary: four with a positive history of drug intake suggestive of causing TTP and three pregnant women.

Table 2 illustrates the initial laboratory parameters of patients.

Disease-related mortality

Three patients (10%) died from their initial disease: One drug-induced patient (ciclosporin) and two idiopathic patients (heavily platelet transfused before their late admission 9 and 10 days from the onset of symptoms) died during the first 24 h. A fourth patient died 48 h after the initiation of the third plasma exchange session from multiple cerebral infarctions. On follow-up, two patients died: a hepatitis C virus (HCV)-positive patient from complications in the context of splenectomy and a second patient with refractory disease from progressive neurological deficiency.

Patterns of response to plasmapharesis

Twenty-two patients (85.6%) achieved remission, with an average of 7.55 plasma exchange sessions, 13 of whom achieved a sustained remission (50%) with an average of six plasma exchanges, whereas four patients (15.3%) were defined as refractory. Another nine patients had 25 relapses (mean 2.7) with an average of nine plasma exchange sessions to achieve remission.

Adjunctive therapies used included steroids in 14 patients (53.8%), azathioprine in 12 (46%), vincristine in seven (27%) and rituximab in one (3.8%). Splenectomy was resorted to in three patients (11.5%).

Overall survival

The 24-month overall survival was therefore 80%. When stratifying survival, excluding the first 24-h mortality of very lately referred cases, the survival would be 24 out of 27 (88.8%). Secondary TTP survival was 85.7%.

Factors associated with relapse

To determine refractoriness/relapse predictors, the 26 patients were classified into two groups according to outcome: group I included 13 patients showing first remission with no relapse and group II included 13 patients showing relapse (nine) or refractoriness (four) within a median follow-up of 2 years. Table 3 illustrates the clinical and laboratory differences between the two groups.

Four patients with relapse (30%) were HCV positive and none of those in remission were HCV positive.

Table 1 Clinical data of the 30 TTP patients

Parameter	No of patients	%
Pregnancy	3	10
Coma	11	37
Positive CT brain findings of infarction	10	30
Diarrhoea	8	27
Fever	8	27
Drug intake	4	13
Family history	3	10
Platelet transfusion before diagnosis	8	27

TTP, thrombotic thrombocytopaenic purpura.

Table 2 Laboratory parameters of all TTP patients after exclusion of the four cases who died in the first presentation

Parameter	Median	Range
Haemoglobin (gm/dl)	9.4	6–12
Platelets ($\times 10^9$/ml)	27.5	9–82
TLC (/μl)	12 900	7–22 000
Reticulocytic count (/μl)	200 000	150 000–300 000
LDH (IU)	865	400–2630

LDH, lactate dehydrogenase; TLC, total leukocytic count; TTP, thrombotic thrombocytopaenic purpura.

The only statistically significant differences between the two groups were in the platelet count and LDH levels ($p<0.05$). There was no correlation between the use of azathioprine or other immunosuppressants and relapse ($r=-0.39$, $p=0.12$).

ADAMTS-13 antigen levels and ADAMTS antibodies were obtained for 12 idiopathic patients at presentation. ADAMTS-13 was reduced in 10 patients (83.3%) and antibodies were recoverable in nine out of 12 patients (75%). There was no correlation between it and the clinical parameters or relapse.

DISCUSSION

To the best of our knowledge, this is the first report on TTP in Egyptian patients with a follow-up period of 2 years addressing the behaviour of the disease, overall survival and factors associated with relapse.

The total survival rate over 2 years was 80%, and the relapse rate was 50%. Only platelet count, LDH level and the need for plasmapharesis sessions were statistically different between those in remission and relapsed or refractory patients. There was no correlation between the use of azathioprine and relapse.

A similar survival rate was seen in the study conducted by Tuncer *et al*[14] when 79% of patients responded but only 28% relapsed in a median of 14 months follow-up. In a study by Dervenoulas *et al*[15] the survival rate in 48 patients was 85%, with a remission rate in 40 months' observation of 76%. Similar results were obtained by many investigators since the

Table 3 Clinical and laboratory differences between the two groups

Parameter	Group I (13 patients) (no relapse), median	Group II (13 patients) (relapse) median	p Value
Age (years)	38 (48)	35 (31)	0.33
Sex	7 men, 6 women	4 men, 9 women	0.34
Diarrhoea	4 patients	3 patients	0.76
Pregnancy	1 patient	2 patients	0.36
Coma	5 patients	4 patients	0.5
Neurological symptoms	4 patients	5 patients	0.34
Fever	4 patients	4 patients	1
Drug intake	3 patients	0 patients	0.34
Family history	1 patient	2 patients	0.76
Time to presentation (median)	5 days	7 days	0.29
Haemoglobin (gm/dl)	9.8	8.9	0.16
Platelets ($\times 10^9$/ml)	45	12	0.03
TLC (/μl)	12 100	13 100	0.19
Reticulocytic count (%)	220 000	250 000	0.38
LDH (IU)	760	970	0.04
Platelet transfusion	2 patients	1 patient	0.8
Immuran	5 patients	9 patients	0.12
Sessions of plasma pharesis (median)	6 sessions	9 sessions	0.02

LDH, lactate dehydrogenase; TLC, total leukocytic count.

establishment of plasmaphaeresis as the cornerstone therapeutic tool.[8 16–18] This is, however, in contrast to the results of Zhan *et al*[11] reporting on the Johns Hopkins Hospital experience from 1992 to 2008 with an all-cause mortality rate of 4% and relapses in 36% of patients during a median follow-up of 30 months, with most (76%) occurring in the first 24 months probably reflecting early diagnosis and more prompt initiation of pheresis.

The increased relapse rate in our study in comparison may reflect ethnic characteristics. In fact, Zhan *et al*[11] found that African-American ethnicity was associated with an increased risk of relapse (OR 4.8, p=0.03). Our patients are considered a mix of African and Arabic ethnicities.

The increased incidence of relapses could also reflect the presence of comorbid conditions, hepatitis C in particular, is highly prevalent in Egypt.[19] Associations between TTP relapses and HCV have previously been reported.[20] In our study 30% of patients with relapse were HCV antibody positive.

Dervenoulas *et al*[15] found that advanced age is associated with treatment failure and poor outcome, but is not of prognostic value regarding the probability of relapse, while Hovinga *et al*[8] reported that among the 47 survivors with TTP no demographic, clinical, or laboratory features were associated with relapse other than male sex. The presence of stupor or coma at the beginning of plasma exchange sessions was an independent predictor of treatment failure, and was the only predictor of mortality from unremitted TTP/haemolytic uraemia syndrome at the beginning of plasma exchange.[21] The current data, however, do not support that coma at the onset is an independent predictor of relapse.

In contrast to our observations, Tuncer *et al*[14] found a significant association between severe thrombocytopaenia, LDH levels (p=0.0199, p=0.047, respectively) and the probability of relapse in a retrospective review of adults with TTP/haemolytic uraemia syndrome treated with plasma exchange. In contrast, Alvarez-Larrán *et al*[22] found that relapsed TTP patients showed lower serum LDH levels than non-relapsed patients (2.2 vs 4.5-fold above the upper limit of normality, p<0.001) in a total of 102 episodes of idiopathic TTP (70 de novo and 32 relapses). Moreover, it was found that de-novo TTP in comparison with relapsed TTP showed a higher haemoglobin level (median 12.2 g/dl versus 9.1 g/dl, p<0.001), while neurological symptoms and fever were less frequently observed in patients with relapsed TTP than in patients with de-novo TTP.[22]

The reported statistical difference and positive correlation between the number of plasma exchange sessions and relapse reflects the severity of the disease. Similar observations were reported by Hwang *et al*.[23]

There was an absence of correlation between the use of azathioprine and the sustainability of remission. The use of immunosuppressants has been advocated for many years but their solid role in preventing relapses has never been consolidated.[10]

The rate of postsplenectomy relapse among patients with relapsing disease was 17%, whereas the non-response rate was 8% for patients with refractory TTP. There were no complications among the 22 laparoscopic cases reported.[20] In the current experience, however, splenectomy was carried out for three patients and was associated with mortality in one patient, concomitantly with HCV.[24]

Although the current series is limited, it gives a good insight into TTP, the risks of refractoriness/recurrence and overall mortality. Early mortality was strikingly high as three patients died during the first 24 h from progressive disease, reflecting very late referral to the centre and highlighting the need for awareness of this disease and its diagnostic criteria. The initial low platelet count and raised LDH would help stratify patients at risk of refractoriness and recurrence who might need a more close follow-up. Larger multicentre studies are needed to build optimised therapies for immunosuppression and standardisation of plasma exchange.

Main messages

- Early referral to a specialised haematology centre can prevent mortality in patients with TTP.
- The initial low platelet count and raised LDH will help stratifying patients at risk of refractoriness and recurrence.

Current research questions

- What is the optimum immunosuppressant treatment to be added to plasmapharesis in refractory TTP?
- What is the optimum duration to continue plasmapharesis after normalisation of the platelet count in TTP patients?
- What is the real impact of HCV on TTP and refractoriness to treatment?

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Competing interests None.

Patient consent Obtained.

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