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THROMBOTIC THROMBOCYTOPENIC PURPURA; AT A TERTIARY CARE CENTRE IN LAHORE, PAKISTAN

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ABSTRACT

Thrombotic thrombocytopenic purpura is a syndrome, characterized by microangiopathic haemolytic anaemia, thrombocytopaenia, neurological symptoms, renal disease and fever. Commonly considered rare, but actually it is one of the most under diagnosed disorders. This study was aimed at evaluating the clinical features, course, prognostic factors and treatment outcome in 17 patients diagnosed as having thrombotic thrombocytopaenic purpura (TTP). It was a cross-sectional descriptive study at Shaikh Zayed Hospital Lahore. This study includes patients diagnosed as having TTP by the department of haematology from January 2005 to December 2007. Eight of 17 patients were treated with plasma exchange. Six of these 8 patients survived. Plasma infusions were performed in 9 patients, 5 of them recovered. Overall 65% patients recovered and mortality was 35%.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare syndrome of unknown aetiology that is characterised by the clinical picture of a microangiopathic haemolytic anaemia, thrombocytopaenia, neurological symptoms, renal disease and fever[1].The disease was first described by Moschcowitz in 1925.[2] Amorosi and Ultmann reviewed 271 cases of TTP. In these patients, treatment with corticosteroids, blood and plasma exchange, plasma infusion, antiplatelet agents, or splenectomy resulted in 46% survival rate.[3]

In the 1980's plasma of patients with chronic relapsing TTP were found to have large multimers of von Willibrand factor vWF unlike normal plasma[2]. Since then many workers have proved that a metalloprotease is required to cleave these large multimers of vWF and this protease is consistently deficient in the plasma of patients with TTP.[4] This deficiency may be a congenitally inherited mutation in the ADAMTS-13 gene as seen in relapsing TTP, or acquired due to the development of autoantibodies against this vWF cleaving protease. Conditions and drugs associated with the development of TTP include HIV, pregnancy, bartonella infection, ticlopidine *etc.*[3,5]

The histological study shows that, TTP is characterized by the presence of intravascular hyaline thrombi composed mainly of platelets with some fibrin in the arterioles and capillaries.[1,6] Many treatment regimens have been employed with varying success, including splenectomy corticosteroids, anti-platelet agents, heparin ,whole blood exchange transfusions, haemodialysis, plasma infusions, vincristine and plasma exchange.

Due to the rarity of this disorder, clinical studies of the treatment of TTP usually includes only a few patients.[7] The literature is particularly devoid of clinical reports studying plasma exchange and plasma transfusions in the treatment of TTP in large number of patients. Although certain clinical findings indicate a poor prognosis in the natural history of patients with TTP, it is important to study these clinical findings to determine if they are still prognostically important in the face of the modern therapy for this disease.

PATIENTS AND METHODS

We included 17 patients in this study who were diagnosed as having TTP according to the classical pentad; microangiopathic haemolytic anaemia, thrombocytopaenia, renal abnormalities, fever and neurological changes. Detailed history and clinical examination were carried out in all patients. Relevent laboratory investigations included CBC, peripheral smear, coagulation profile, D-dimer, liver function tests (LFT's), renal function tests (RFT's), LDH, viral serology and autoimmune profile were carried out in all patients. Special investigations eg CT brain, ultrasonograghy were performed whenever required. Eight of 17 patients were treated with plasma exchange. The mean frequency of plasma exchange was 4 sessions. The procedure was carried out using Baxter continuous flow cell separator through catheters placed in the central venous line / anticubital veins. In all the patients 2-3 litres of plasma was exchanged for fresh frozen ABO- and Rh- compatible plasma. The procedure

required two to three hours to exchange the desired amount of plasma.

A complete response to therapy was defined as the resolution of the following indices after treatment with plasma exchange or plasma infusion for at least 3 months. An increase of the platelets to more than $150x10^9$ per litre, a normal peripheral blood smear and normal results on neurological examination. To be eligible for evaluation of response, patient had to be observed for at least three months after therapy.

The collected data of patients was entered into SPSS version 10 for analysis. Chi sq. test and wilcoxin rank sum were used for statistical analysis. P value of ≤0.05 was considered as cut off point for statistical significance.

RESULTS

Case series included 17 patients, 6 males and 11 females. Mean age was 50 years for males and 29 years for females. At presentation 15 of 17 patients had neurological symptoms ; 10 (59%) had fluctuating sensorium and were dysoriented in time and space, 5 (29%) had recent history of fits, 5 (29%) developed aphasia and 3 (18%) progressed to coma. Fever was seen in all patients, 11 patients (64%) presented with bruising and petechiae whereas 7 (41%) developed overt bleeding during hospital stay. Splenomegaly was noted in 2 patients. Demographic and clinical features are shown in Table 1.

Table 1: *Symptoms and signs in 17 patients of TTP.*

Sr. No.	Signs and Symptoms	Frequency (%)
1.	CNS symptoms a) headache b) fits c) fluctuating snsorium d) aphasia e) coma	15 (88%) 08 05 10 05 03
2.	Fever	17 (100%)
3.	Malaise	13 (76%)
4.	Petechiae	09 53%)
5.	Bleeding	11 (64%)
6.	Splenomegaly	02 (12%)

On analysis of different haematological parameters it was found that haemoglobin ranged from 3.5 to 13 g/dl at presentation (mean 8.4 g/dl). Total leucocyte count ranged from 2.5 x 10^3/ul to 37 x 10^3/ul (mean 11 x 10^3/ul). Platelet count was subnormal in 14 of 17 patients (mean 54 x 10^3/ul), rest of 3 patients had a normal platelet count at admission but had a falling trend in following days. Schistocytes were seen in peripheral smear in all the 17 patients. PT and APTT were elevated significantly in 6 and 8 patients respectively. All patients had mild to moderate elevation of D-dimer but 9 of them progressed to overt secondary DIC with markedly increased D-dimer (>2000 ng/ml) during course of disease (Table 2).

Biochemical analyses revealed increase in LDH in all patients with a mean value of 1933 u/l. Mean serum creatinine was 3.3mg/dl and mean BUN was 60mg/dl. Total Bilirubin was elevated in 8 of 17 patients (mean 3.3 mg/dl) while hepatic enzymes (ALT, AST) revealed mild to moderate elevation in all cases (Table 2).

Table 2: *Pretreatment laboratory data of 17 patients of TTP.*

Sr No	Lab value	Mean value	Median value	Ref value
1.	Hb	8.4	8.0	11.5-17g/dl
2.	TLC	11.2	8.2	4-11x109/l
3.	Platelet	55	37	150-400x109/l
4.	PT	14.3	14	12-14 sec
5.	APTT	36.6	36	28-32 sec
6.	LDH	1933	1406	100-190u/dl
7.	Creatinine	3.3	1.9	0.3-1.2mg/dl
8.	BUN	60	54	6 -18mg/dl
9.	Bilirubin	3.3	2.2	0.1-0.9mg/dl

Table 3: *Initial pretreatment features in 17 patients of TTP.*

Sr. No.	Lab Finding	Present In
1.	Schistocytes	17 (100%)
2.	D dimmer > 2000	9 (53%)
3.	Protienuria	10 (59%)
4.	RBC in urine	8 (47%)
5.	WBC in urine	9 (59%)

Different haematological and biochemical parameters were compared in survivors and non-survivors and analysed for any significant association with mortality (Table 4). Although all lab parameters were more deranged in non-survivor group, elevated serum LDH and BUN levels in nonsurvivors were found to be statistically significant ($p \leq 0.05$).

Association of TTP with different underlying clinical conditions was analysed. In 7 of 11 female patients it was secondary to pregnancy related conditions ie after normal vaginal delivery (in 4), IUD (in 2), after ruptured tubal pregnancy (in 1). One female patient developed TTP after hysterectomy, she had a relapse after 6 months. One male and 3 female patients were known cases of auto-immune disorders (RA and SLE). Fourth patients were Hepatitis C positive. In a male patient TTP was associated with acute necrotising pancreatitis & in other 3 with respiratory and urinary tract infections.

Plasma exchange was done in 8 of 17 patients. Six of these patients survived. Nine patients received plasma infusions alone. Five of these 9 patients recovered. Overall 65% patients survived and mortality was 35%. There was no statistically significant difference in outcome in patients treated with plasma exchange or plasma infusion (p value 0.43). However the patients who received more than 3 sessions of plasma exchange had improved outcome in terms of survival (p value 0.03) (Table 5).

Six patients received aspirin and one of them also received clopidogrel as a part of treatment. Eleven of 17 patients were given corticosteroids. No patient had splenectomy.

Table 4: *Association of patients age and lab data with outcome in TTP.*

Sr No	Variable	Mean value in Survivors (n = 11)	Mean value in Non survivors (n = 6)	p-value
1.	Age (yrs)	36	38	0.70
2.	Haemoglobin (g/dl)	8.8	7.9	0.39
3.	Total leukocyte count (n x 10^3/ul)	12.4	9.6	0.48
4.	Platelets (/ul)	61,000	45,000	0.44
5.	PT(sec)	14	15	0.12
6.	LDH (u/l)	1402	2690	0.05*
7.	T.bilirubin (mg/dl)	3.2	3.5	0.83
8.	Creatinine (mg/dl)	3.1	3.6	0.79
9.	BUN (mg/dl)	43	87	0.04*

* : p value is statistically significant (≤0.05)

Table 5: *Association of clinical variable with outcome in TTP.*

Sr no	Variable		Survivors (n=11)	Nonsurvivors (n=6)	p-value
1.	Gender	Male	3	3	0.38
		Female	8	3	
2.	Fluctuating Sensorium	Yes	5	5	0.14
		No	6	1	
3.	Bleeding	Present	7	4	0.90
		Absent	4	2	
4.	Ddimer >2000	Present	5	3	0.86
		Absent	6	3	
5.	Plasma Exchange (PE)	Yes	6	2	0.43
		No	5	4	
6.	Plasma infusion (PI)	Yes	5	4	0.43
		No	6	2	
7.	>3 sessions of PE	Yes	5	0	0.03*
		No	1	2	

* : p value is statistically significant(≤0.05)

DISCUSSION

This study retrospectively assessed 17 cases of TTP diagnosed over 3 years. The study adopted homogeneous diagnostic criteria with the principal aim of evaluating the clinical and haematological features of TTP and limiting any bias. The diagnosis was made with classical pentad. In fact, in majority of the patients with TTP, some negative events such as renal dysfunction, infection and severe haemorrhagic patterns often made it

Table 6: *Patients, TTP characteristics and outcome.*

Patient	Sex	Age	Diagnosis	TTPindex	Plt min	Ldh max	Symptoms	Therapy	Outcome
1.	F	25	SVD	120	10	1207	CNS.K.B.F	PI	S
2.	F	20	SVD	44	27	1191	CNS.K.B.F	PI	NS
3.	M	22	URTI	32	37	1200	CNS.K.B.F	PI	NS
4.	F	26	Hepatitis C	16	76	1188	CNS.K.B.F	PI	S
5.	M	50	SLE	175	20	3500	CNS.K.F	PE	NS
6.	F	40	Postop sepsis	62	37	2300	CNS.K.F	PE	S
7.	F	18	SLE	20	72	1450	CNS.K.B.F	PE	NS
8.	M	60	Pancreatitis	202	4	811	CNS.K.F	PI	NS
9.	F	50	UTI	168	6	1006	CNS.B.F	PE	S
10.	F	25	SLE/Abortion	400	15	6000	CNS.F.B	PI	NS
11.	F	25	IUD/PIH	50	37	1841	K.F.B	PI	S
12.	F	28	IUD	108	13	1406	CNS.F.B	PI	S
13.	F	20	SLE/SVD	47	84	3973	CNS.F.B	PI	NS
14.	M	20	HepC	200	10	2000	CNS.F	PE	S
15.	F	25	SLE	50	30	1500	CNS.K.B.F	PE	S
16.	M	75	URTI	70	23	1600	CNS.K.F	PE	S
17.	M	56	HepC	130	11	1430	K.F	PE	S

F: female, M: male, SVD: simple vaginal delivery, SLE: systemic lupus erythematosis, UTI: urinary tract infection, IUD: intrauterine death, PIH: pregnancy induced hypertension, URTI: upper respiratory tract infection, CNS: central nervous system abnormalities, F: fever, K: deranged kidney function, B: bleeding, plt: platelets, PI: plasma infusion, PE: plasma exchange, S: survived, NS: not survived

difficult to consider TTP as an emerging primary diagnosis.

Study also outlined the demographic features and frequency of different sign and symptoms in such patients. In our experience gender and age did not seem to have an impact on incidence of TTP. This is probably due to the relatively small number of patients in our study but we should not rule out the possibility that different combinations of the above-mentioned factors could favour the occurrence of TTP.

Patients with severe symptoms, such as the presence of seizures, paraesthesias, paresis, aphasia, mental status changes, or coma, did less well than patients with mild symptoms. This is like other clinical studies, in which it was found that patients with certain clinical factors did less well than other patients with TTP.[8]

The current study also found a correlation between elevated LDH peak values and BUN during the course of TTP and a worse prognosis of TTP ($p > 0.05$). Surprisingly, neither a high TTP index at TTP diagnosis nor other lab parameters, seemed to correlate with a worse prognosis.

There was no significant difference in outcome in patients treated with plasma exchange or infusion in our study. According to some studies plasma exchange, has recently been proved to be more effective than plasma infusion,[9,10] as it is capable of eliminating the large von Willebrands factors or some endogenous endonucleases which can induce apoptosis of the damaged endothelial cells. Where analysing TTP outcome in our series, it is important to note that our study included a small number of patients in a limited period of time. One problem with small clinical series that have used the multiagent approach in treating TTP, is that the interpretation of results is difficult. However our study showed an improved outcome in patients with TTP treated with plasma exchange when it was carried out in a number of sessions i.e. >3 (p 0.03). We emphasize that any delays in diagnosing TTP could have decreased treatment efficacy. Furthermore plasma exchanges were not always timely or continuously performed, owing to management difficulties in many centers. Bearing this in mind, a better, ongoing relationship between physician, haematology team and the blood transfusion services should be established for optimal management of patients with TTP.

Mortality rate attributable to thrombotic microangiopathy is highly variable in the literature,

ranging from 33 to 73%.[11,15] The high rate (35%) of TTP-related mortality in our series is noteworthy, albeit expected, given that the majority of our deceased patients had severe TTP. Furthermore, the high percentage of patients receiving Plasma infusion or Plasma exchange late after diagnosis in our study could have been a bad prognostic factor per se, leading to TTP-related mortality.

For four decades after the initial description of thrombotic thrombocytopenic purpura by Moschcowitz in 1925, this unusual syndrome led to death in almost all cases.[1] Although some patients with TTP had a more prolonged clinical course (chronic TTP), the vast majority of cases showed an acute course sometimes leading to death in hours or days. Some of the early therapeutic efforts included splenectomy and the use of corticosteroids and heparin.[7,l] The use of antiplatelet agents such as aspirin, dipyridamole, or dextran has met variable success.[8]

The first breakthrough in the treatment of TTP was the use of whole blood exchange transfusions. This method of treatment was first attempted by Rubinstein and colleagues,[2] and the patient recovered. Bukowski and co-workers reported 13 patients who were treated with exchange transfusions, 7 of whom had remissions This report was followed by that of Pisciotta and associates, which confirmed that about 50% of patients with TTP could survive when treated with exchange transfusions.[2]

As plasma exchange technology was developed, it was successfully applied in the management of patients with TTP. Although this technique has been studied alone and in combination with a variety of other therapies-such as corticosteroids, haemodialysis, splenectomy, antiplatelet agents, and vincristine. Most of these clinical series have had a small number of patients, usually fewer than 10.[13] The multiagent approach has been successful in many clinical series, but it offers no clear answers regarding which treatment methods are most important.

The report of patients with TTP treated at the Cleveland Clinic Foundation represents the largest number of patients treated with plasma exchange or exchange transfusions at a single institution[1]. It therefore presents a group of patients treated in a relatively uniform manner, and it allows the efficacy of plasma exchange and exchange transfusion to be studied.[1] The study concluded that plasma exchange is an important treatment modality significantly improving the outcome. The majority of patients treated before 1975 were treated with exchange transfusions.[2,3,14]

The mechanism underlying the therapeutic success of different treatment methods remains speculative, in part because many clinical series have a multiagent approach in treating TTP. It may be that the effects of plasma exchange and whole blood exchange transfusions are related to the removal of a soluble toxic material.[5] Alternatively, the addition of a deficient "plasma factor" or a dilutional effect by the transfusion of whole blood or plasma in plasma exchange may be the crucial factor in the successful treatment of TTP.[3,6,15]

Treatment with plasma exchange has substantially improved the prognosis of patients with TTP. There are no clearly prognostic clinical findings, and even patients with severe initial clinical findings may respond well to aggressive treatment. The mechanism of the benefit of plasma exchange remains mainly speculative, as does the question of whether additional therapeutic modalities will improve an 88% rate of response to plasma exchange.[5]

As regard the treatment of TTP, there are a few promising reports about the use of defibrotide,[16-20] which seems to have a considerable antithrombotic effect due to its profibrinolytic activity.[21,22] This is based on its ability to induce release of plasminogen activator factor from the vascular tissue[23] and to decrease blood concentration of plasminogen activator inhibitor.[24] These and other defibrotide-related effects, the most important of which concerns inhibition of platelet aggregation, have recently been acknowledged to be of benefit to post-BMT veno-occlusive disease,[25] that, like TTP, can occur as a result of endothelial damage.

In **conclusion**, our study suggests the opportunity for earlier diagnosis, more careful clinical monitoring and the need for future studies on TTP, which appears to be a rare but often life-threatening condition.

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