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Original Article

Internal Medicine Section

A Study of Haematological and Haemostasis Parameters and Hypercoagulable State in Tuberculosis Patients in Northern India and the Outcome with Anti-Tubercular Therapy

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ABSTRACT

Introduction: Tuberculosis is one of the leading infectious diseases with high morbidity and mortality in the developing countries. Tuberculosis is also rarely associated with hypercoagulable state and very limited literature is available on this association.

Aim: To study the haematological and haemostasis laboratory parameters, to correlate the abnormalities for a hypercoagulable state and to study the outcome with anti-tubercular therapy.

Materials and Methods: The study population included 128 patients with newly diagnosed tuberculosis. Anti-tubercular therapy naïve patients were studied for haemostasis parameters like Prothrombin time, Activated Partial Thromboplastin time, Factor VIII, Fibrinogen and D-dimer and haematological parameters like Haemoglobin, White Blood Cells, Platelet count, Erythrocyte Sedimentation Rate (ESR), Lactate Dehydrogenase, C-reactive protein and albumin. At the end of the second month of anti-tubercular therapy, results were compared and analysed using statistical package for the social sciences software (SPSS).

Results: Prothrombin levels were deranged in 50%. Activated Partial Thromboplastin time levels were deranged in 18%. Deranged Factor VIII levels were found in 35.15%. Fibrinogen levels were deranged in 57%. D-Dimer positivity was found in 57.8% patients. Anaemia was found in 75.78%, Leukocytosis in 49.21%, Thrombocytopenia in 37.5% and Hypoalbuminaemia in 75%. ESR levels were raised in 98.43%. Follow up comparison analysis revealed significant p-value for all the parameters except Factor VIII and Activated Partial Thromboplastin time. Similar trend was also observed within different groups of Tuberculosis patients.

Conclusion: Tuberculosis does favour a hypercoagulable state with increased risk of developing thrombosis and significant improvement with the anti-tubercular treatment alone.

Keywords: Inflammation, Infarction, Meningitis, Thrombosis

INTRODUCTION

India has the highest annual incidence of Tuberculosis (TB) and is estimated at 1.98 million, one fifth of the global incidence [1]. TB is often associated with hypercoagulable state. Deep Venous Thrombosis (DVT) can be confirmed with radiological methods in 3.4% of patients with TB [2]. The real incidence may however be higher because it is clinically not diagnosed in most patients [3]. Vascular thrombosis in TB patients is considered an infrequent event and not much literature and research is available worldwide on this association and very few isolated case studies have been undertaken in India. There are few case studies which have shown the development of DVT in patients of pulmonary tuberculosis and also some other thromboembolic phenomenon like Inferior Vena Cava obstruction and cerebral venous and arterial thrombosis in different categories of tuberculosis patients [4,5]. Decreased anti-thrombin III (AT III), decreased Protein C (PC) and thrombocytosis, increased platelet aggregation and elevated plasma fibrinogen levels appear to induce a hypercoagulable state in TB which improves with treatment as seen in various studies [6,7].

This study was an extensive clinical study with a large number of Tuberculosis patients being investigated and analysed for hypercoagulability and this is a first such large study from India to the best of our knowledge.

MATERIALS AND METHODS

The prospective interventional study was conducted in the Department of Medicine, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, from February 2011 to April 2012. Ethical Clearance was obtained from institutional protocol ethics committee.

Inclusion Criteria: Patients more than 12 years of age and newly diagnosed with Tuberculosis of any site and not yet started on anti-tubercular therapy.

Exclusion Criteria: The following patients were excluded: Patients with history of past vascular thromboembolic disorder, presence of cardiovascular disease, diagnosed or suspected autoimmune disorder, neoplasm, trauma or surgery during the last six months, patients on anticoagulant or immunosuppressive agents, bed ridden for more than two weeks, pregnant females.

A written informed consent was taken from all the patients prior to their inclusion in study. All patient underwent complete clinical assessment followed by requisite radiological, biochemical and Acid Fast Bacilli (AFB) examination, followed by the haemostasis parameters like Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), factor VIII (FVIII), fibrinogen and D-dimer and haematological parameters like haemoglobin (Hb), White Blood Cells (WBC), platelet count, Erythrocyte Sedimentation Rate (ESR), Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP) and albumin. All the patients were further divided into four subgroups according to the site of TB namely pulmonary, Central Nervous System (CNS), disseminated and others group where the group entitled 'others' consisted of extrapulmonary organ limited TB other than CNS like pleural effusion, abdominal, lymphadenitis etc.

Coagulation profile was done for all patients. It included PT, APTT, Fibrinogen, Factor VIII level estimated by standardized methods. A 2.7 ml blood was drawn in a trisodium citrate anticoagulant vial. The blood samples were centrifuged for 15 min at 3000 rpm and plasma was collected in eppendorf tubes. Plasma was stored in -80 degree Fahrenheit refrigerator till use. Samples were analysed within 48 hours for PT, APTT, Fibrinogen and FVIII levels by the standardized procedures using RecombiPlastin Tin 2G kit. D-dimer was done using latex agglutination test.

Anti-tubercular therapy had standard dose regimen as per recommended by the Stop TB Department of the World Health Organization i.e. daily drug dose of Isoniazid 5 (4–6) mg/kg body weight, Rifampicin 10 (8–12) mg/kg body weight, Pyrazinamide 25 (20–30) mg/kg body weight and Ethambutol 15 (15–20) mg/kg body weight and Streptomycin 15 (12-18) mg/kg body weight.

At the end of second month of ATT these haemostasis parameters and haematological profile were repeated along with the clinical outcome during these two months of intensive therapy.

Reference range taken for result analysis were: Hb – Male (13.3-16.2 g/dl), Female (12.0-15.8 g/dl), WBC/TLC (3.54-9.06x 10^3/mm^3), Platelet count (1.65-4.15x10^5/mm^3), LDH (115-221 U/L), Albumin (4-5 mg/dl), ESR–Male (0-15 mm/hr), Female (0-20 mm/hr), PT (≤ 03 seconds), International Normalized Ratio (INR) (0.8-1.2), APTT (≤ 05 seconds); Factor VIII (50-150%), Fibrinogen (200-400 mg/dl).

A statistical evaluation was carried out to determine the associations and correlations in the patients with tuberculosis by student's t-test, paired t-test using SPSS software.

RESULTS

The study enrolled total of 128 patients and 56 (44%) were male and 72 (56%) were female patients. Mean age was 31.55±15.03 years with a range of 12-75 years [Table/Fig-1]. Comparison study analysis was done in 88 tuberculosis patients as out of 128 patients initially included in the study, 14 patients met with mortality and 26 patients were lost to follow up during the follow up period of two months.

Site Of TB.	Male	Female	Total	Lost To Follow Up	Total No. With Full Follow Up
Pulmonary	24	15	39	12	27
CNS	08	29	37	17	20
Disseminated	09	13	22	08	14
Others	15	15	30	03	27
Total	56	72	128	40	88

[Table/Fig-1]: Distribution of patients according to type of Tuberculosis.

HAEMATOLOGICAL PARAMETERS

In the study population, highest Hb was 15.6 g/dl and lowest was 2.2 g/dl. Out of total 128 patients 97 (75.78%) had anaemia, of which 44(78.57%) males and 53(73.61%) females were anaemic. Highest WBC was 30.6x10^3/mm^3 and lowest was 1.3x10^3/mm^3. Of the total patients, 63 (49.21%) had leukocytosis and 05 (3.90%) had leukopenia. Highest Platelet count in the study population was 6.39x10^5/mm^3 and lowest was 0.24x10^5/mm^3. Of the total patients 15 (11.71%) had thrombocytosis and 48 (37.5%) had thrombocytopenia. Highest ESR was 110 mm/hr and lowest was 12 mm/hr. A total of 126 patients (98.43%) had raised ESR levels.

Highest albumin was 5 mg/dl and lowest was 2 mg/dl. Out of total 128 patients 96 (75%) had hypoalbuminaemia. Maximum LDH level was 1100 U/L and minimum was 340 U/L. Baseline LDH was raised in all 128 patients. CRP positivity was found in only 13 (10.15%) patients.

Comparison study analysis was done in 88 tuberculosis patients and follow up comparison analysis results revealed significant p-value for all parameters Hb, WBC, platelet count, CRP, LDH, albumin. Within different groups of TB patients namely pulmonary, CNS, disseminated and others similar result pattern was seen with significant p-value for all parameters in the follow up analysis study [Table/Fig-2,3].

HAEMOSTASIS PARAMETERS

In the study population highest PT was 26.60 sec and lowest was 10.20 sec. Out of total 128 patients 64 (50%) had PT within normal

Parameters	Baseline	After 2 Months ATT	p-value
Haemoglobin (g/dl)	10.87±2.17	11.72±1.79	<0.01
WBC (X10^3/cu.mm)	9.24±4.27	7.93±1.40	.006
Platelet Count (X10^5/cu.mm)	2.56±1.38	2.07±.33	.001
ESR (mm/hr)	61.43±21.10	8.34±4.29	<0.01
LDH (U/L)	753.92±183.39	205.70±42.11	<0.01
Albumin (mg/dl)	3.45±.65	3.83±.38	<0.01

[Table/Fig-2]: Comparisons of haematological parameters with follow up in Tuberculosis patients.
p-value is considered significant when it is <0.05

Parameters	Pulmonary			CNS			DISSEMINATED			OTHERS		
	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value
Haemoglobin (g/dl)	10.36±2.08	11.29±1.73	<0.01	10.85±2.29	11.75±1.92	<0.01	11.25±1.52	11.84±1.34	.024	11.21±2.46	12.09±1.95	<0.01
WBC (x10^3/cu.mm	10.58±5.62	8.19±1.26	.040	9.52±4.07	7.78±1.55	.082	8.61±3.56	7.94±1.53	.545	8.00±2.69	7.77±1.37	.648
Platelet count(x10^5/cu.mm	2.5±1.48	2.02±.28	.058	2.22±1.10	1.95±.263	.312	2.94±1.37	2.21±.53	.054	2.60±1.47	2.12±.26	.122
ESR (mm/hr)	73.89±10.00	7.59±1.67	<0.01	50.90±24.44	7.70±3.67	<0.01	58.07±18.52	10.79±7.26	<0.001	58.52±22.81	8.30±4.30	<0.01
LDH (U/L)	783.37±188.84	201.33±25.64	<0.01	764.64± 182.99	205.15± 32.65	<0.01	758.86±194.73	208.07±31.65	<0.001	714.00± 175.46	209.26±62.94	<0.01
Albumin (mg/dl)	3.47±.64	3.83±.30	.001	3.70±.59	3.97±.50	.029	3.20±.65	3.73±.32	.002	3.36±.68	3.76±.37	.001

[Table/Fig-3]: Comparison of haematological parameters with follow up across different Tuberculosis groups.
p-value is considered significant when it is <0.05

range while equal number of 64 (50%) patients had deranged PT levels. Highest INR was 2.82 and lowest was .74. Highest APTT was 41.50 sec and lowest was 20.00 sec. Out of total 128 patients 23 (18%) had deranged APTT levels. D-Dimer positivity was found in 74 (57.8%) patients out of total study population of 128. Highest fibrinogen level was 999.70 mg/dl and lowest was 124.10mg/dl. 73(57%) had deranged fibrinogen levels out of which 62 (48.43%) had high fibrinogen levels while 11(8.59%) had low fibrinogen levels. Highest FVIII level was 312.40% and lowest was 35.50%. In the study population, 45 (35.15%) had deranged FVIII levels out of which 36(28.12%) had high levels of FVIII and 09(7.03%) had low levels.

In our post follow-up comparison analysis for 88 patients for haemostasis parameters, p-value was significant for PT and Fibrinogen studies. F VIII and APTT revealed non-significant p-value. Across different groups of TB patients p-value revealed similar pattern for all parameters except in disseminated group where the p-value was non-significant for parameter PT also along with APTT and FVIII [Table/Fig-4,5].

Parameters	Baseline	After 2 months ATT	p-value
PT (second)	3.427±3.55	0.92±2.33	<0.01
APTT (second)	-0.327±3.75	-0.76±2.04	0.334
Fibrinogen (mg/dl)	391.43±167.34	272.23±92.66	<0.01
Factor VIII (%)	125.08±72.83	126.21±37.65	0.893

[Table/Fig-4]: Comparison analysis for PT, APTT, Fibrinogen and Factor VIII in Tuberculosis patients.
p-value is considered significant when it is <0.05

decreased stainable iron in erythrocytes (hypochromia) [14]. Chronic inflammation also decreases the erythropoiesis leucopoiesis and megakaryopoiesis, ultimately developing pancytopenia [15]. The prevalence of leukocytosis in our study has been observed to be greater than that reported in other studies which could be attributed to large number of subjects being acutely ill patients with sepsis and acute inflammatory state. The ESR is increased by any cause or focus of inflammation. ESR levels significantly decreased following 2 months of ATT.

The mechanism of hypoalbuminaemia in acute infectious disease is known to be related with poor oral intake of protein, decreased synthesis of protein from the liver, increased catabolism of protein, and increased metabolism of albumin due to the vascular leakage of serum protein because of increased vascular permeability [16]. LDH is often used as a marker for haemolysis and is a non-specific marker for inflammation. Hypoalbuminaemia is a powerful predictor of mortality and morbidity in various conditions [17-19]. In this study hypoalbuminaemia was seen across all four types of tuberculosis but it was more marked in disseminated and miliary tuberculosis and in hospitalised subjects. LDH parameter was raised in all subjects.

C-reactive protein is an acute-phase reactant protein found in the blood and its level rise in response to inflammation [20,21]. Multiple studies have shown that peripheral blood mononuclear cells in TB produce abundant IL-1,IL-6 and tumour necrosis factor-α (TNF-α) [22]. It is also reported that TB might enhance the local production and release of pro-inflammatory cytokines which in turn reduces the fibrinolytic activity [23]. Additionally these cytokines induce hepatic acute phase responses that alter levels of coagulation proteins such as fibrinogen and factor VIII [24,25]. These widespread disturbances

Parameters	Pulmonary			CNS			DISSEMINATED			OTHERS		
	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value	Baseline	After 2 months	p-value
PT (seconds)	3.31±3.45	1.17±2.49	<0.01	4.42±3.80	1.01±2.47	<0.01	2.22±2.05	2.02±3.40	0.08	3.25±4.01	0.38±1.95	<0.01
APTT (seconds)	0.12±4.54	-0.60±1.97	0.44	0.32±4.46	-1.71±2.09	0.07	-1.47±1.90	-0.50±1.85	0.20	- 0.37±2.75	-0.25±2.03	0.85
Factor VIII (%)	133.89±75.41	119.80±21.04	.298	100.08±58.79	124.88± 24.80	.080	121.44±80.90	142.02±76.64	.526	136.68± 74.53	125.43±27.12	.431
FIBRINOGEN (mg/dl)	421.43±141.94	294.84± 109.52	.001	368.90± 172.16	241.79± 33.47	.003	417.17±191.47	292.58± 120.66	.058	364.77± 176.50	261.62±83.99	.020

[Table/Fig-5]: Comparison with follow-up for PT, APTT, Factor VIII and Fibrinogen across different Tuberculosis groups.
p-value is considered significant when it is <0.05

DISCUSSION

TB is one of the oldest diseases known and is caused by bacteria *Mycobacterium tuberculosis* and it usually affects lungs, although multiple other organs can also be affected. Anaemia was reported in 16% to 94% in patients with pulmonary TB. Many reports suggest TB as one of the differential diagnoses of anaemia [8-10]. Anaemia occurred in a large number of patients (75.78 %) in our study, but it had a benign course in most cases. In multiple studies prevalence of anaemia has been found to be more in females than males [11]. In our study male (78.57%) subgroup showed relatively more prevalence of anaemia than and the female subgroup (73.61%). TB-associated anaemia improved significantly with anti-TB treatment in almost all patients who followed up after the intensive phase of ATT. Multiple pathogenetic mechanisms have been indicated for anaemia in TB, but many studies have shown suppression of erythropoiesis by inflammatory mediators as an important cause of anaemia [12,13]. Chronic inflammation results in hyperplastic mononuclear phagocytic system and is responsible for extravascular haemolysis and also the trapping of free iron. This eventually results in in homeostasis lead to activation of vascular intima and render it more thrombogenic [26]. Thus TB is characterized immunologically by an acute–phase response and haematologically by impaired fibrinolysis consistent with a hypercoagulable state. DVT is significantly (four times) higher in patients with a fibrinogen level over 05 g/l [27]. The mechanism of platelet hyper-aggregability seen in most cases is unclear. Increased platelet activity may be a response to inherent differences in platelet reactivity among the population, organ infarction, vascular changes, hormonal and autocrine factors such as plasma catecholamines [28-30]. It has been suggested that platelet activation occurs in TB patients and there is a good correlation between platelet activation and the extent of the disease [31]. Plasma fibrinogen which is the functionally important ligand for glycoprotein IIB/IIIA and it also causes platelet aggregation. A large epidemiological study by Meade et al., showed that the plasma fibrinogen concentration is an important determinant of platelet aggregation [28]. The hyper-fibrinogenaemia as observed in 48.43% in our study might have a correlation with the thrombocytosis seen in 11.71% patients in this study.

Turken et al., studied 45 patients with newly diagnosed active pulmonary TB and 20 healthy volunteers as the control groups and were investigated and evaluated for possible role of haemostasis disturbances leading to hypercoagulability in pulmonary TB and patients were found to have anaemia, thrombocytosis, albuminaemia, increased ESR, LDH, CRP, Fibrinogen, Fibrin Degradation Products (FDPs) and plasminogen activator inhibitor1 (PAI I) and decreased AT III. This favoured a state of hypercoagulability which gradually improved with anti-tubercular therapy [6]. Robson et al., also studied haemostasis changes in patients of pulmonary TB favouring a hypercoagulable state [7].

The factor VIII level is elevated in hepatic necrosis, because factor VIII is made in hepatocytes and released as they are destroyed; factor VIII is reduced in DIC because of the thrombin-induced generation of activated PC, which proteolyses factor VIII. Slowly evolving DIC primarily causes venous thromboembolic manifestations e.g., deep venous thrombosis, pulmonary embolism and abnormal bleeding is uncommon. In severe, rapidly evolving DIC, skin puncture sites (e.g., Intravenous or arterial punctures) bleed persistently, ecchymosis form at sites of parenteral injections and serious bleeding manifestations may occur [32,33]. So, in this study high D-dimer and increased fibrinogen and factor VIII were observed. Majority of these patients had simultaneous PT/APTT derangement and D-dimer positivity with associated thrombocytopenia with normal liver function tests and no bleeding manifestations favouring state of slowly evolving DIC which itself can have thromboembolic manifestations.

Lan et al., reported occurrence of infarct in 47% of Taiwanese patients of tuberculous meningitis [34]. Koh and coworkers reported cerebral infarction in 22% patients [35]. Anuradha et al., studied predictors of stroke in patients of tuberculous meningitis and stroke occurred in 30% of cases with tuberculous meningitis [36]. Chan et al., studied 40 TBM patients for cerebral infarcts complicating tuberculous meningitis. They observed cerebral infarction in 30% of the patients. In nine patients, infarcts were symptomatic and in three patients they were silent [37]. In our study we found cerebral infarcts in 6 patients of TBM, out of which 3 patients died and 3 patients improved.

In the study, it was noted that irrespective of p-value the baseline haematological and haemostasis parameters improved significantly in majority of patients when compared with the same parameters post 02 months of ATT.

CONCLUSION

Patients were found to have anaemia, thrombocytosis, albuminaemia, increased ESR, LDH, Fibrinogen, Factor VIII levels and D-dimer favouring a state of hypercoagulability which gradually improved with anti-tubercular therapy. Thus TB does favour a hypercoagulable state with increased risk of developing thrombosis with significant improvement in the above mentioned parameters with the anti-tubercular treatment. Also, it can be concluded that a patient with tuberculosis can present with varied haematological manifestations and thus a proper search for tuberculosis should be undertaken in all cases of refractory anaemia and other haematological manifestations, especially in a country where tuberculosis is prevalent. These parameters can also be followed up as a useful monitor of progression and resolution of the disease process.

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