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Blood Coagulation Changes among Sudanese Patients with Pulmonary Tuberculosis

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Abstract: ***Objective:*** ***To assess the blood coagulation changes in patients with Pulmonary Tuberculosis (PTB).*** ***Methodology:*** ***Fifty Patients with PTB were included in this study, in addition to 10 apparently healthy individuals as internal control group. Coagulation parameters of prothrombin time (PT), activated partial thromboplastin time (APTT), (TT), Platelet count, Hb concentration and ESR were measured in each patient.*** ***Results:*** ***The mean values for coagulation measures for cases compared to controls were 15.4 ± 1.9 compared to13.4 ± 0.5 for PT (P < 0.002), 34.3±4.7 compared to 30.2 ± 6.5 for APTT (P < 0.02), 13.4±1.5 compared to 13.1 ± 0.9 for TT (P < 0.6), 384,500 ± 153,000 compared to 259,400 ± 94,000 for platelets (P < 0.001), 11.2 ± 1.7 compared to 13.6 ± 1.6 for HB (P < 0.001) and 75.7 ± 26 compared to 16 ± 9 for ESR, respectively.*** ***Conclusion:*** ***PTB is associated with prolongation of PT, APTT, thrombocytosis, anemia and elevated ESR.***

Keywords: Tuberculosis, Sudanese, Blood coagulation

1. Introduction

Tuberculosis (TB) is second only to Human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) as the greatest killer worldwide due to a single infectious agent. In 2011, 8.7 million people fell ill with TB and 1.4 million died from TB. Over 95% of TB deaths occur in low- and middle-income countries. Tuberculosis (TB) is caused by bacteria (*Mycobacterium Tuberculosis*) that most often affect the lungs [1]. Pulmonary Tuberculosis (PTB) is one of the most prevalent chronic infectious diseases among poor communities [2]. PTB causes bleeding disorders. Hematologic abnormalities have been described in association with mycobacterial infections for almost 100 years. Patients with both pulmonary and extra-pulmonary tuberculosis (TB) may demonstrate peripheral blood abnormalities and findings may be minimal or profound [3,4]. Heamoptysis is one of the major presentations related to vascular walls disorders. A number of earlier studies reported the occurrence of thrombotic complications, particularly disseminated intravascular coagulation and deep vein thrombosis, in tuberculosis (TB) patients. The aberrant expression of tissue factor (TF), the primary activator of coagulation cascade, is known to be responsible for thrombotic disorders in many diseases including bacterial infections [5,6].
However, severe infection and inflammation almost invariably lead to hemostatic abnormalities, ranging from insignificant laboratory changes to severe disseminated intravascular coagulation (DIC). Therefore, the objective of this study was to assess the burden of PTB on blood coagulation among Sudanese.

2. Materials and Methods

This is a descriptive prospective (cross sectional) study conducted in El Obeid Hospital to assess blood coagulation parameters changes that linked to infection with *Mycobacterium Tuberculosis*. Fifty Patients with confirmed diagnosis of PTB were included in this study, in addition to 10 apparently healthy individuals as internal control group. PTB diagnosis was confirmed after clinical assessment, chest X-ray, and positive Zeil-Nelson (ZN) stain. Coagulation parameters of prothrombin time (PT), activated partial thromboplastin time (APTT), (TT), Platelet count, Hb concentration and ESR were measured in each patient.

2.1 Ethical consent

Each participant was asked to sign a written ethical consent form during the interview, before the specimen was taken. The informed ethical consent form was designed and approved by the ethical committee of the Faculty of Medical Science Research Board, University of Kordofan, Sudan.

2.2 Statistical analysis

SPSS version 16 statistical software was used for statistical analysis. The numeric results (PT, APTT, TT, Platelet count, Hb concentration and ESR) were expressed as mean±SD, and the 95% confidence intervals (CIs) of the means were calculated. The X test was used to compare the differences in categorical variables between the groups. Relationships between variables were analyzed using Pearson's correlation analysis. A $p<0.05$ was considered statistically significant.

3. Results

In this study, the effects of PTB on coagulation parameters were evaluated in 50 patients with PTB (cases), in addition to 10 apparently healthy individuals (controls). The male female ratio was 2.33: 1.00.

Description of the study population according to their complains related to coagulopathy is shown in Fig1., however, the great majority presented with heamoptysis.

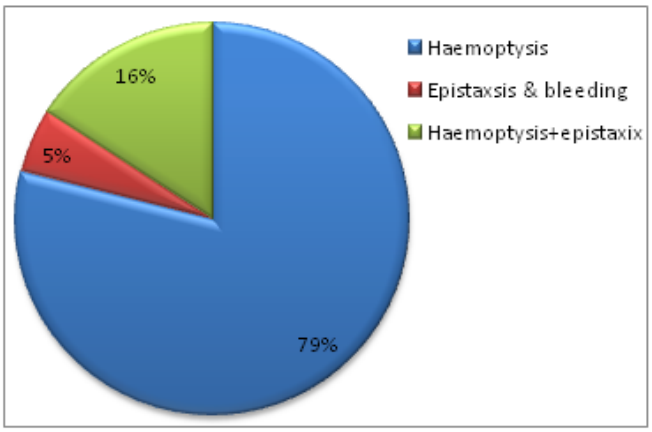

Figure1. Patients with symptoms related to coagulopathy

The mean values for coagulation measures for cases compared to controls were 15.4 ± 1.9 compared to13.4 ± 0.5 for PT (P < 0.002), 34.3±4.7 compared to 30.2 ± 6.5 for APTT (P < 0.02), 13.4±1.5 compared to 13.1 ± 0.9 for TT (P < 0.6), 384,500 ± 153,000 compared to 259,400 ± 94,000 for platelets (P < 0.001), 11.2 ± 1.7 compared to 13.6 ± 1.6 for HB (P < 0.001) and 75.7 ± 26 compared to 16 ± 9 for ESR, respectively, as indicated in Table1.

Table 1: Distribution of the study subjects by Mean ± SD of the coagulation parameters

Variable	Mean ± SD		
	Cases	Controls	P value
PT	15.4 ± 1.9	13.4 ± 0.5	0.002
APTT	34.3±4.7	30.2 ± 6.5	0.02
TT	13.4±1.5	13.1 ± 0.9	0.6
Platelets count	384,500 ± 153,000	259,400 ± 94,000	0.001
HB	11.2 ± 1.7	13.6 ± 1.6	0.001
ESR	75.7 ± 26	16 ± 9	0.0001

Furthermore, 80% and 44% of the cases were found with prolonged PT and APTT, respectively, compared to only 11% and 20% of the controls in this order. Consequently, high platelets count, High ESR levels and low Hb concentration were identified in 54%, 98% and 70% of the cases respectively, compared to 0%, 20% and 20% of controls correspondingly, as indicated in Figure 2.

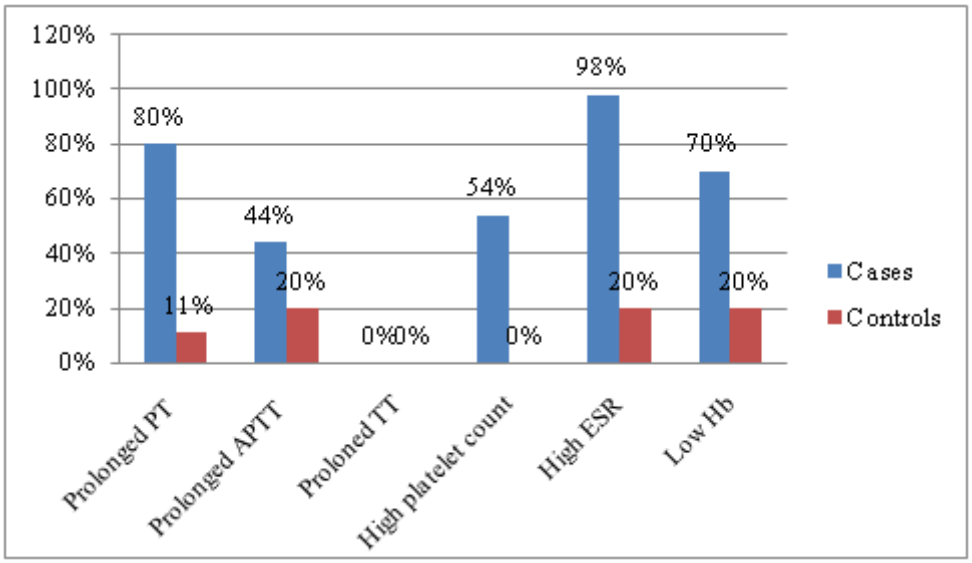

Figure 2: Description of the Study subjects by coagulation parameters.

4. Discussion

Sudan is a large poor country in Africa with a miscellaneous population and long history of civil wars, as well as with a healthcare system located under considerable strain. Therefore, the country has a high burden of tuberculosis (TB) with an estimated 50,000 incident cases during 2009, when the estimated prevalence was 209 cases per 100,000 of the population [7]. The present study was performed in one state (North Kordofan State), which is the first study from Sudan to find out the subsequent effect of PTB on blood coagulation, to establish policies to be considered in the management of patients with PTB.

Activation of coagulation and fibrinolytic pathways in response to various bacterial infections are critical components elicited by both pathways [8-10]. Immune complexes and many other factors elaborated in various infectious diseases are shown to induce pro-coagulant tissue factor (TF) expression in monocytes/macrophages and the endothelium, which under normal healthy state doesn't expressed TF [11-13].

As indicated in the results PT, APTT and TT showed significant prolonged times among cases compared to controls with exception of TT (the length was not significant) with increased platelets count. Such findings were previously reported [14].

Analysis in patients with active PTB showed anemia, leucocytosis, thrombocytosis, elevation in plasma fibrinogen, factor VIII, plasminogen activator inhibitor 1 (PAI-1) with depressed antithrombin III (AT III) and protein C (PC) levels [15]. Platelet aggregation studies demonstrated increased platelet activation [14]. Severe pulmonary tuberculosis (PTB) is often complicated by deep venous

thrombosis (DVT). Because of the association between inflammation and haemostatic changes that can result in a hyper-coagulable state [15]. However, infection triggers both pro-inflammatory and anti-inflammatory host responses, the magnitude of which depends on multiple factors, including pathogen virulence, and the immune response after recognition of danger signals derived from microorganisms. This is further exploring the role the cytokine response, the coagulation cascade and their multidirectional interactions [16].

However, many theories have been proposed for these blood coagulation disorders. Systemic inflammation results in activation of coagulation, due to tissue factor-mediated thrombin generation, down regulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. Pro-inflammatory cytokines play a central role in the differential effects on the coagulation and fibrinolysis pathways [17]. Several studies have reported thrombotic complications in TB patients, particularly disseminated intravascular coagulation (DIC) [18,19]. However, it is unclear how tuberculosis infection causes thrombotic complications in some patients as mycobacteria are not known to produce endotoxins or exotoxins that are known to initiate the clotting cascade. Although, limited number of studies in the past has shown that *in vitro* infection of monocytes with mycobacterial components can induce production of the pro-inflammatory cytokines and increases the pro-coagulant activity [20], there is little information on the regulatory pathways and molecular mechanisms responsible for increased TF expression during mycobacterial infections. Earlier studies have reported that cell wall components of *Mycobacterium* species induced TF expression in macrophages, but these studies were limited to the use of derivatives from non-virulent *Mycobacterium* species [21,22]. Exposure of human monocyte-derived macrophages (MDMs) to live *Mtb* or gamma-irradiated Mtb H37Rv (γ-Mtb) led to a marked induction of TF in monocyte derived macrophages (MDMs), predominantly in the CD14+ macrophage subpopulation [23].

Coagulation disorders such as DIC, initiated by massive tissue destruction and endothelial injury leads to the release of tissue factors, which triggers widespread thrombus formation in the microcirculation [24]. This further exacerbates endothelial injury by depleting coagulation factors and platelets while also activating the fibrinolytic system, resulting in a consumptive coagulopathy [25]. Fragmentation of erythrocytes generates schistocytes and hemolysis. Elevated D-dimers, thrombocytopenia, a prolonged PT, partial thromboplastin time, and thrombin time, and decreased fibrinogen levels are typically noted [26].

Although, there is a lack of studies that measures all these hematological parameters among PTB, but there are reasonable evidences of correlation between these parameters and PTB [27,28].

In conclusion, there is a significant alteration in coagulation parameters (particularly PT and APTT) of pulmonary tuberculosis patients. Hematological parameters should be considered in the subsequent management of patients with PTB.

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