International Journal of Virology and AIDS

Akpotuzor et al. Int J Virol AIDS 2014, 1:1
ISSN: 2469-567X

Research Article: Open Access

Prognostic Value of Some Acute Phase Reactants in the Management of Pulmonary Tuberculosis Disease

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Abstract

This study was conducted to assess the relevance of serum C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), relative plasma viscosity (RPV) and fibrinogen level in the management of pulmonary tuberculosis (PTB) disease. One hundred (100) PTB patients attending the TB clinic of Dr Lawrence Henshaw Memorial Specialist Hospital Calabar, and 70 age and sex-matched apparently healthy subjects between 15-65 years of age were selected and enrolled. Standard techniques were used for the assays. Results showed significantly lower PCV ($p<0.05$) in PTB patients (0.35 ± 0.07L/L) when compared with control subjects (0.44 ± 0.04L/L). CRP, ESR and RPV showed significantly higher values in PTB patients (71.09 ± 60.34mg/L, 60.81 ± 38.33mm/hr and 2.11 ± 0.79 respectively) than in control subjects (2.86 ± 0.70mg/L, 7.25 ± 4.00mm/hr and 1.74 ±0.32 respectively). Among PTB patients who were smear positive, serum CRP and ESR were highest in those with AFB 3+ (140 ± 12.30mg/L and 80.15 ± 32.81mm/hr respectively) and least in those with AFB 1+ (18.63 ± 31.01mg/L and 46.91 ± 38.19mm/hr respectively). Furthermore, CRP (125.31 ±29.57, 44.48 ±40.57, 13.57 ± 10.17 and 5.99 ± 3.17mg/L) and ESR (87.30 ± 28.64, 58.27 ± 35.77, 26.70 ±16.47 and 18.78 ± 8.57mm/hr) decreased significantly ($p<0.05$) as anti-tuberculosis therapy progressed from 0-7months. However, the rate of decline in CRP was more distinct than that of ESR. Significant lower values of ESR, RPV and CRP with significant higher PCV were observed in PTB patients without cavity lesions when compared with their counterparts with cavity lesions This study therefore concludes that among the analyzed possible markers of systemic inflammatory response in PTB, serum CRP has been observed to be the most sensitive in defining disease severity and indicating a response to treatment.

Keywords

Pulmonary tuberculosis, Prognostic value, Acute phase reactants, Rheology

Introduction

Pulmonary tuberculosis (PTB) has remained a major air-born disease over the years. Its high morbidity and mortality continue to evoke concerns of global magnitude, especially among international health bodies notably the World Health Organization (WHO). Even more disturbing is the current trend of emerging multidrug-resistant strains of the causative organism; *Mycobacterium tuberculosis* [1]. Interestingly, it has been observed that a high percentage of new TB cases and its associated deaths occur in developing countries with its socio-economic toll on society as it primarily affects people during their most productive years [2]. The need for adherence to standard treatment regimen in addition to prompt and accurate diagnosis has been highlighted as necessary steps towards effective management as well as control of tuberculosis. However in the developing countries where incidentally new cases of the disease have continued to emerge, poor resources alongside political instability have further complicated PTB management giving rise to the emphasis on treatment monitoring [3,4]. The pathophysiology of PTB more or less involves inflammatory responses by the host that may result in a rise in the concentration of acute phase proteins in the patient's blood. This could in turn result in alterations in rheologic properties of the blood hence the consideration for using related parameters in the review of disease severity. Against this backdrop, several parameters are being explored for their possible prognostic value in the management of TB. So far, several studies have confirmed changes within PTB patients [4-6]. Among these parameters are the indicators of acute phase response which mainly comprise Erythrocyte Sedimentation Rate (ESR) and serum C - reactive protein (CRP) concentrations. Other markers with possible prognostic value in PTB management include haemorrheologic parameters such as Relative Plasma Viscosity (RPV), Fibrinogen level as well as Packed Cell Volume (PCV).It is therefore the aim of this work to provide information on the changes in these acute phase response parameters that would be useful in the management of PTB patients in resource-constrained regions where advanced technology for effective fellow up in pulmonary tuberculosis is not readily available.

Materials and Methods

One hundred (100) out of 123 male and female pulmonary tuberculosis patients aged between fifteen and sixty five years, attending the TB clinic of Dr Lawrence Henshaw Memorial Specialist Hospital, Calabar were enrolled for the study after obtaining approval from the Cross River State Ministry of Health Research Ethics Committee. Twenty-three (23) were excluded due to HIV

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Citation: Akpotuzor JO, Ekarika EA, Akwiwu EC (2014) Prognostic Value of Some Acute Phase Reactants in the Management of Pulmonary Tuberculosis Disease. Int J Virol AIDS 1:002

Received: September 02, 2014: **Accepted:** November 14, 2014: **Published:** November 16, 2014

Table 1: Serum CRP, ESR, RPV and PCV of pulmonary tuberculosis patients and control subjects.

	Subjects		
Parameters	**PTB patients n=100**	**Controls N=70**	**P-value**
CRP (mg/L)	71.09 ± 60.34	2.86 ± 0.70	0.000
ESR (mm/hr)	60.81 ± 38.33	7.25 ± 4.00	0.000
RPV	2.11 ± 0.79	1.74 ± 0.32	0.000
PCV (L/L)	0.35 ± 0.07	0.43 ± 0.04	0.000

Table 2: Serum CRP, ESR, RPV and PCV of pulmonary tuberculosis patients based on AFB load.

	Acid Fast Bacillus load				
	0 (No AFB/100 fields) n = 42	**1+ (10-99 AFB/100 fields) n=11**	**2+(1-10 AFB/ field in at least 50 fields) n=23**	**3+ (>10AFB/ field in at least 20 fields) N=24**	**P - value**
CRP(mg/L)	19.58 ± 31.91	48.03 ± 43.12	112.45 ± 40.50	132.15 ± 27.91	0.000
ESR (mm/hr)	30.45 ±17.80	30.73 ±18.04	90.87 ± 22.77	98.92 ± 24.21	0.000
RPV	1.67 ± 0.49	1.70 ± 0.48	2.10 ± 0.46	3.15 ± 0.53	0.000
PCV (L/L)	0.40 ± 0.0	0.39 ± 0.07	0.31± 0.07	0.29 ± 0.05	0.000

Table 3: Serum CRP, ESR, RPV and PCV of pulmonary tuberculosis patients based on duration of treatment.

	Duration of treatment				
Parameters	***Newly n=46**	**2 Months n=22**	**5 Months n=23**	**7 Months n=9**	**P - value**
CRP (mg/L)	125.31 ± 29.57	44.48 ± 40.57	13.5710.17	5.99 ± 3.17	0.000
ESR (mm/hr)	87.30 ± 28.64	58.27 ± 35.77	26.70 ±16.4	18.78 ± 8.57	0.000
RPV	2.56 ± 0.81	2.02 ± 0.52	1.62 ± 0.42	1.28 ± 0.26	0.000
PCV (L/L)	0.31 ± 0.07	0.37 ± 0.05	0.40 ± 0.04	0.43 ± 0.04	0.000

Categories were based on the treatment phase of Directly Observed Therapy

Newly: stands for newly diagnosed PTB patients

co-infection and other disease conditions. Subjects were diagnosed as pulmonary tuberculosis patients based on the presence of the acid bacilli in their sputum smear together with the X-ray findings. Biodata and medical history from their case notes include Sex, age presence/absence of HIV co-infection, X-ray findings as well as treatment documentations of these patients. Seventy (70) age and gender-matched apparently healthy individuals (with no history of tuberculosis) served as control subjects in the research. They were randomly selected from residents of Calabar. Informed consent was sought and obtained from all participants. Pack cell volume and erythrocyte sedimentation rate was analyzed by standard techniques ICSH, 1993 [7]. The relative plasma viscosity was by Reid and Ugwu [8] method, while the estimation of fibrinogen concentration was by kit method based on Clauss method [9] purchased from BAUR Company USA. The quantitative determination of C- reactive protein was by enzyme immunoassay method. Acid-fast bacilli (AFB) Load was graded according to number of bacilli per field in accordance with WHO standard. The data generated from this work were subjected to student's t test and one way analysis of varience (ANOVA) using SPSS 17.0 Statistical tool package. A two tailed P-value of < 0.05 was considered indicative of a statistically significant difference.

Results

Serum C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR), relative plasma viscosity (RPV) and packed cell volume (PCV) of pulmonary tuberculosis patients in Calabar were measured in this study. The mean values and standard deviations of these parameters for both PTB patients and control subjects are shown in Table 1. Mean serum CRP, ESR and RPV values were significantly higher ($p<0.05$) in PTB patients than in control subjects while mean PCV values for control subjects was significantly higher ($p<0.05$) than those of PTB patients when comparison was made using student's t test analysis. On the other hand Serum CRP, ESR and RPV values using ANOVA showed significant differences ($p<0.05$), increasing with higher acid fast bacilli(AFB) loads while mean PCV values decreased significantly ($p<0.05$) with higher AFB loads (Table 2). Forty six (46) out of the 100 PTB patients were newly diagnosed, 22 had been on drug therapy for 2 months, 23 for 5months and 9 for 7 months. While the mean serum CRP, ESR and RPV values showed significant decreases ($p < 0.05$), the PCV values showed significant increases ($p<0.05$) using ANOVA as duration of drug therapy progressed (Table 3). Comparison between the mean values of serum CRP,ESR,PCV and RPV obtained for PTB patients having cavity lesions and those without cavity lesions as shown by their radiologic findings is shown in table 4. Significant lower values of ESR, RPV and CRP with significant higher PCV were observed in PTB patients without cavity lesions when compared using student's t test with their counterparts with cavity lesions.

Discussion

In this study, serum C-reactive protein concentration, erythrocyte sedimentation rate (ESR), and relative plasma viscosity (RPV), in addition to packed cell volume (PCV) were evaluated as acute phase reactants and rheologic parameters. The prognostic value of these possible markers was assessed in relation to AFB load together with their change in levels in the course of treatment as well as their radiologic findings. Data collected from this study demonstrated significantly lower ($p<0.05$) PCV value (0.35 ± 0.07L/L) in PTB patients than in control subjects (0.44 ± 0.04L/L). Similar findings were reported from this locality and have been attributed to the cytokine mediated reduction in erythropoietin secretion and reduced responsiveness of the erythroid precursors to the hormone as well as impaired mobilization of iron from macrophages during inflammatory processes [4]. On the other hand, mean ESR and RPV values (60.81 ± 38.33mm/hr, 2.11 ± 0.79 respectively) of PTB patients obtained in this study were significantly higher ($p<0.05$) than control values (7.25 ± 4.00mm/hr, 1.74 ±0.32 respectively) as shown in table 1. It is attributable to increased levels of fibrinogen concentration seen in PTB patients; a trend observed in previous works across Nigeria [4,10,11].

Serum- CRP is a common acute phase reactant protein used as indicator of systemic inflammation resulting from infection or injury. It has been proposed as a biomarker that can differentiate severe infections like pneumonia, sepsis and lower respiratory tract infections from self-limiting illnesses [6]. In this study, it was hypothesized that serum CRP concentrations, although a non-specific maker, could be useful as a marker of extent or severity of pulmonary tuberculosis (PTB). Significantly higher ($p<0.05$) mean serum CRP values (71.09 ± 60.34mg/L) found in PTB patients than in control subjects (2.86 ± 0.70mg/L) is in agreement with an earlier report from Abeokuta, Nigeria [6]. This elevated concentration of serum CRP is unequivocal evidence of an active tissue-damaging process as seen in the pathogenesis of PTB. It was also observed in this study that the follow-up patients had significantly lower ($p<0.05$) ESR and serum CRP concentrations than active pulmonary tubercular patients at initial stage of diagnosis (Table 3). This indicates that as anti-tubercular drug therapy progressed, the levels of these parameters decreased. Interestingly, although the significant decrease in ESR is indicative of a resolution in the systemic inflammatory process, it was slower in its fall rate. This probably is due to the fact that ESR is merely an indirect method of assessing acute phase changes by measuring the rate at which erythrocytes fall through plasma; a phenomenon largely dependent on plasma concentrations of fibrinogen. The half-life of fibrinogen has been reported to be much longer than that of many other acute phase proteins including CRP [12], which may explain the relatively slow fall in ESR that occurred among the patients as drug therapy progressed. By contrast, IL-6, the principal cytokine that induces CRP synthesis, rapidly decreases in concentration in the serum of patients treated for PTB as observed by Lawn and co-workers (1999). Perhaps this rapid decrease is contributed to by the very short half-life of CRP in the circulation [12].This was reflected in the rapid, significant reduction ($p<0.05$) in mean serum CRP concentration observed in the majority of the follow-up patients examined in this study, dropping to almost as low as the level for control subjects, at the 7th month of therapy. This finding indicates that the concurrent fall in serum CRP concentrations and ESR during treatment of PTB patients correlates with the resolution of the systemic inflammatory

Table 4: Serum CRP, ESR, PCV and RPV of pulmonary tuberculosis patients based on X-ray findings.

	X ray findings		
Parameters	**Cavity lesions (n=66) Mean ± SD**	**Non cavity lesions (n=34) Mean ± SD**	**P-value**
PCV (L/L)	0.33 ±0.07	0.40 ± 0.06	0.000
ESR (MM/HR)	74.54 ± 37.61	34.15 ± 22.60	0.000
RPV	2.27 ± 0.80	1.80 ± 0.67	0.004
CRP (MG/L)	91.78± 56.53	45.91± 30.91	0.000

process and this is especially so with serum CRP concentrations. Pepys& Hirschfield (2003) [13], had earlier observed that serum CRP was especially useful as a good marker, indicating a response to the treatment and can even point out potential defaulters in drug treatment. Significantly higher mean values ($p<0.05$) of serum CRP, ESR, and RPV in PTB patients presenting with cavitary lesions (91.78 ± 56.53mg/L, 74.54 ± 37.61mm/hr 2.27 ± 0.80) was observed when compared with those without cavitary lesions (45.91 ± 30.91mg/L, 34.15 ± 22.60, 1.80 ± 0.67) (Table 4). Pulmonary destruction as evidenced by tuberculous chest cavitations signifies disease and hence the higher levels of CRP, ESR and RPV concentrations of patients with cavitations than those without. These data emphasis the usefulness of CRP, ESR and RPV especially, as sensitive markers in the definition of disease severity as the level of rise in the group with cavitations was over twice as high as that of those without cavitations. However, the pack cell volume of the PTB patents without chest cavity lesions was significantly higher when compared with those with chest cavitations.

The control of tuberculosis remains a global challenge with Nigeria being one of the countries in sub-Saharan Africa noted to have a high prevalence of the disease occurrence. Interestingly, the main goal of Nigeria's TB program has been to half the TB prevalence and death rate by 2015 in line with the Millennium Development Goals. Whether this laudable goal remains achievable presently, is a thought worth reconsidering. However, a positive turn in the proper management and effective control of the disease could be achieved by incorporating C-reactive protein assay in the management of pulmonary tuberculosis particularly in resource-constrained regions.

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