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DRUG INDUCED HEMATOLOGICAL DISORDERS IN PATIENTS ON ANTITUBERCULOSIS DRUGS IN THE SOUTH WEST REGION OF CAMEROON.

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ABSTRACT

Background: Antituberculosis drugs (ATD) have been known to efficiently combat *Mycobacterium tuberculosis* either due to the active principle itself or to its metabolites. The first line treatment regimen of tuberculosis (TB) patients which involves the intensive and continuation phase have been known to have some adverse effects. This study was carried out in the South West Region of Cameroon to determine the magnitude of drug induced hematological disorders (DIHD) in TB patients under treatment. **Methods:** Ninety six TB patients on ATD were enrolled and compared to 32 (control) individuals who were neither on ATD or any other treatment. In this hospital based cross sectional study, consenting participants records were reviewed for medical history and questionnaire issued. About 2ml of venous blood was collected and analyzed using automatic hematological analyzer. **Results:** DIHD was observed in 62 (64.58%) of the 96 patients as compared to 5/32 (15.63%) of the control group (p= 0.00000157). In the 62 patients, a combination of drug induced hematological disorder was recorded: 35 (56.45%) had agranulocytosis, 24 (38.71%) leucopenia, 23 (37.1%) anemia and 17 (27.42%) thrombocytopenia. Gender (p=0.173), age (p=0.461) and treatment duration (p=0.448) were not associated with DIHD. **Conclusion:** TB patients who receive standard ATD treatment do develop drug induced hematological disorders, with agranulocytosis the most commonly observed. Close monitoring of such patients is advocated, since as patients with agranulocytosis have been known to usually have a high risk of optimistic infections and will recommend that the dosage.

KEYWORDS: Antituberculosis drugs; Hematological disorders; Agranulocytosis; South West Region, Cameroon.

INTRODUCTION

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive.[1] Tuberculosis mostly affects young adults, in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment.[1] The latest incidence of tuberculosis (per 100,000 people) in Cameroon was 243.00 as of 2011. Over the past 21 years, the value for this indicator has fluctuated between 112.00 in 1990 and 320.00 in 2003. Worldwide, this incidence has also increased, bringing back TB as a reemerging disease.[2]

An effective control of tuberculosis has been achieved by the widespread use of antituberculosis drugs such as such as isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.[3] Recommended by WHO through the DOTS (directly observed treatment, short-course) strategy.[4] However, antituberculosis drugs have been shown to induce various adverse conditions.[5, 6] although they efficiently combat the microorganism either due to the active principle itself or to its metabolites.[7,8] Tuberculosis (TB) could be fatal if left untreated, however, adverse effects of anti-TB medications (anti-TBs) themselves may limit treatment.[5]

Drug-induced hematologic disorders are generally rare adverse effects associated with drug therapy. The patients who had any hematological alteration due to anti-tuberculosis drugs may have had weaker natural and acquired (cell-mediated) immunologic response to tuberculosis infection, and more vulnerable bone marrow cells and hepatic cells to anti-tuberculosis drugs.[9] The mechanisms of drug-induced hematologic disorders are the result of direct toxicity or an immune reaction.[10]

The incidence of idiosyncratic drug-induced hematologic disorders varies depending on the condition and the associated drug. Drug toxicity on hematopoietic cells is usually mediated through intermediate metabolites that bind to proteins and DNA to cause bone marrow failure. Genetic variation leads to variability in the presence of these reactive metabolites and explains the idiosyncratic nature of these sorts of drug reactions.[11,12] Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality.[13] This study therefore focus to determine the magnitude of drug induced hematological disorders in patients on anti-tuberculosis drugs in the South West Region of Cameroon. The prevalence of various hematological disorders associated to antituberculosis drugs.

MATERIALS AND METHODS

Study Area

The study was conducted in south west region of Cameroon. Buea is located about 800 m above sea level in Mount Cameroon. Buea, the capital of the SW region is located on the eastern slopes of Mount Cameroon and has a population of over 200,000. It lies at latitudes 4.09 °N and longitudes 9.13 °E and has a total surface area of 870 km2. Limbe is another important town in the region and formally known as Victoria, it is a natural resource coastal city situated at 4.00 °N and 9.11 °E. It covers a surface area of 549 km2 and situated near the Atlantic Ocean. Limbe has an equatorial climate and is dominated by the tropical equatorial rainforest with tall trees.

Study Population

The study focused on Tuberculosis patients who lived and visited Tuberculosis centers in hospitals and clinics in the study area. The TB patients on treatment between one and three months were controlled patients who visited the Centers for routine checkup and their medication. Non-Tuberculosis most especially medical healthy individuals who were neither on antituberculosis drug or any other medication in the study area served as a control group.

Study Design

A hospital based cross-sectional study was carried out from January to June 2015 to determine the prevalence of Drug-induced Hematologic Disorders in patients on Antituberculosis Drugs in the South West Region of Cameroon. The control group had participants who were neither on antituberculosis drug or any other drug that could affect blood cells.

Data Management and Analysis

During data collection completed questionnaires were checked regularly to rectify any discrepancy, logical errors or missing values. Participants data obtained were entered into a log book and later keyed into a computer using Microsoft excel 2013 and verified for the possibility of entering errors. Data were coded, entered and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Categorical variables using their frequency and percentage and Chi-square test was used to test level of significance at p-value <0.05 considered statistically significant.

Data Collection

Participants with hepatitis, HIV, Kidney failure, metabolic disorders of any kind or condition that could lead to abnormality in uric acid level were excluded from studied group. The control group had participants who were neither on antituberculosis drug or any other drug that could alter blood cells.

After obtaining consents from the participants, hospital records were reviewed for medical history and a structured questionnaire was administered by trained personnel to collect clinical information, dietary habits and socio-demographic characteristics.

Specimen Collection and Laboratory Procedures

About 2ml of venous blood was collected from eligible participants in EDTA Tube labelled with unique identification codes. The sample was then analyzed using Automatic Hematologic analyzer to determine the various blood cell.

RESULTS

A total of 96 tuberculosis patients were enrolled in the study: 59 (61.5%) of the 96 patients where male and 37 (38.4%) were female and their ages ranges from 21-80 years. Fifty (52.08%) were between the ages of 21-30 years, 14 (14.58%) between the ages of 31-40 years, 23 (23.96%) between 41-50 years and 9 (9.38%) of ages 51-80 years. the majority of patients was between the age range of 21-30 years and the least between 51-80 years.

Thirty two people who were neither on antituberculosis drug or any other drug that could affect blood cells constituted the control group. The mean age of participants in the control group was 30.26years and their ages ranged from 21– 42 years.

The prevalence of hematological disorders in the studied and control group was 64.58% (62/96) and 15.63% (5/32) respectively (χ^2 = 23.061, p = 0.00000157) (Table 1).

Table I: Prevalence of hematological disorders in the studied group and control group.

	Hematological Disorder		Total	P Value
	Present	Absent		
Studied Group	62/96 (64.58%)	34/96 (34.52%)	96	<0.001
Control Group	5/32 (15.63%)	27/32 (84.37%)	32	
Total	67	61	128	

Of the 96 study subjects, 35/59(59.3%) male and 27/37 (73%) female developed hematological disorders. Comparison of both groups showed no statistical significance (χ^2 = 1.853, p=0.173) (Table 2).

Of the 62 participants who developed DIHD majority 35 (56.45%) were between the age group of 21-30 years, while the least 4(6.45%) was > 50 years. Also 39/62 (62.90%) were on treatment ≤ 2months compared to 23/62 (37.10%) who were on treatment > 2 months. (Table2).

Table 2: Association of Hematological disorders to Gender, Duration of treatment and Age

	Hematological Disorder		P Value
	Present	Absent	
Gender			
Male	35/59 (59.32%)	24	0.1951
Female	27/37 (73%)	10	
Total	62	34	
Duration of Treatment			
≤ 2 months	39/62(62.90%)	24	0.5060
> 2 months	23/62(37.10%)	10	
Total	62	34	
Age			
21-30	35 (56.45%)	15	0.4609
31-40	8 (12.90%)	6	
41-50	15 (24.20%)	8	
> 50	4 (6.45%)	5	
Total	62	34	

The prevalence of the combination of various types of drug induced hematological disorders is shown in Figure 1. Of the 62 patients the most frequent DIHD was agranulocytopenia seen in 35/62 (56.45%), followed by leucopenia 24/62 (38.71%), anaemia 23/62 (37.10%) and thrombocytopaenia 17/62 (27.42%). Agranulocytopenia in this study, was defined as neutrophil granulocytes count less than 1.38 x109/L (45% of WBC). Leucopenia was defined as total white blood cell count less than 3,500 cells/mcL. Thrombocytopenia was defined as platelet count less than 150,000 /mcL while anemia was defined as decrease in hemoglobin below 13.5g/dl for male or 12g/dl in female.

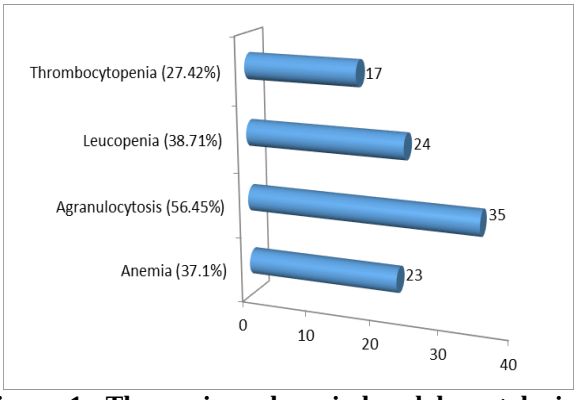

Figure 1: The various drug induced hematological disorders observed among the study participants.

Also of the 62 patients diagnosed with DIHDs who altogether presented 99 cases of the various types of DIHDs, majority 32/62 (51.61%) presented just a single disorder compared to 30/62 (48.39%) who developed multiple disorders (Table 3).

Table 3: Prevalence of Single and Multiple Hematological disorder

Hematological disorders	Number of patients (%)
Single	
Anemia	12/62 (19.35%)
Agranulocytopenia	9/62 (14.52%)
Leucopenia	3/62 (4.84%)
Thrombocytopenia	8/62 (12.90%)
Total	32/62 (51.61%)
Multiple	
Agranulocytopenia + Leucopenia	15/62 (24.19%)
Agranulocytopenia + Anemia	3/62 (4.84%)
Agranulocytopenia + Thromboctopenia	2/62 (3.23%)
Anemia + Leucopenia	1/62 (1.61%)
Anemia + Thrombocytopenia	3/62 (4.84%)
Agranulocytopenia +Anemia + Thrombocytopenia	1/62 (1.61%)
Agranulocytopenia + Anemia + Leucopenia	2/62 (3.23%)
Agranulocytopenia + Leucopenia + Thrombocytopenia	2/62 (3.23%)
Agranulocytopenia + Leucopenia + Thrombocytopenia + Anemia	1/62 (1.61%)
Total	30 (31.25%)

DISCUSSION

Hematological disorders arise through a variety of mechanisms and etiologies. Drug-induced hematological disorders can span almost the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system. The wide spectrum of drug-induced hematologic syndromes is mediated by a variety of mechanisms, including immune effects, interactions with enzymatic pathways and direct inhibition of hematopoiesis. Drug-induced syndromes include hemolytic anemia, red cell aplasia, sideroblastic anemia, megaloblastic anemia, polycythemia, aplastic anemia, leukocytosis and others. There are four possible relationships of tuberculosis to hematologic disease. Drugs may cause idiosyncratic reactions, malabsorption, interference with iron metabolism, and hemolysis in patients with red blood cell enzyme deficiencies. Idiosyncratic reactions manifested by depression of any or all of the three cellular blood elements (white cells, red cells and platelets) together with the coagulation system may be caused by any of the anti-tuberculosis drugs.[14, 15]

In this study the higher prevalence of drug induced hematological disorder observed in the studied group is most likely a consequential effect of the anti-tuberculosis drugs taken by the studied patients. This goes further to buttress the fact that anti-tuberculosis drugs has the potential of inducing hematological disorders as indicated by Arbex *et al*.[16] and Aliasghar*et al*.[17]

Also of the 96 studied participants, 28.13% female and 36.45% males developed hematological disorders. This proportion is similar to that reported by Ghulam *et al.*,[18] Majority of the studied participants (40.63%) who developed hematological disorders were on treatment ≤ 2months compared to 23.95% who were on treatment > 2 months. Eyuel *et al.*, in their study noted that the levels of hemoglobin, hematocrit and platelet count of the TB patients were significantly lowered after completion of 2 months intensive phase of TB treatment.[19] The majority of the 62 participants who developed drug induced hematologic disorder in our study were between the age group 21-30 years (56.45%) while the least 14.52% were > 50 years. This shows that tuberculosis infection is still a serious public health issue especially among younger generation.[20]

In this study, majority (33.33%) of the patients with drug-induced hematological disorders presented just a single disorder compared to 31.25% who developed multiple hematologial disorders. This is higher compared to that of Shishido *et al.*[21] that reported a prevalence of 1.18% single and 1.11% of multiple hematological disorders but it supports the findings that most of the patients presented more single compared to multiple hematological disorder.

The most frequent manifestation of drug induce hematological disorders was agranulocytopenia with 35.35%. Agranulocytopenia in this study, was defined as Neutrophil granulocytes count less than 1.38 $x10^9$/L. Shishido *et al* .[21] reported a prevalence of 0.06% of agranulocytosis due to isoniazid and rifampicin while Kyoung *et al*.[22] reported the first case of agranulocytosis due to ethambutol. Reason while ours was higher could be because of lack of monitoring of our patients.

We also observed a prevalence of 24 % leucopenia, which has also been reported by Nagayama *et al*.[9] who had an incidence of 2.36% of leucopenia due to the Antitiberculosis drugs. The wide spectrum of drug-induced hematologic disorders is mediated by a variety of mechanisms, including immune effects, interactions with enzymatic pathways, and direct inhibition of hematopoiesis.[23]

Leucopenia may occur in the course of treatment with anti-tuberculosis drugs, but it is not necessary to stop the chemotherapy immediately, because the WBC count recovers spontaneously or remains under stable leucopenic state during chemotherapy in most cases

Furthermore, we also observed 17.17% of thrombocytopenia which was defined as platelet count less than 150,000/mcL, Kant and collegues.[24] reported the first case of thrombocytopenia which was also later reported by Surya *et al*.[25] This supports our study that anti tuberculosis drugs cause drug induced hematological disorder. Thrombocytopenia is a serious side effect that is potentially caused by anti-TB drugs which occurs mostly due to rifampicin (RIF).[26] The main mechanisms of thrombocytopenia are decreased production or increased destruction of platelets. The drug binds non-covalently to membrane glycol-proteins to produce compound epitopes or induce conformational changes which antibodies are specific. In addition, RIF-dependant antibodies attach to thrombocytes and cause increased destruction.[27] Vancomycin can also be associated with marked thrombocytopenia and demonstrable drug-dependent antibodies in the serum.[28]

About 23.23% patients in our study were anemic, which was defined as decrease in the amount of hemoglobin concentration below 13.5g/dl for male or 12g/dl in female. There are generally two types of drug induced anemia that is hemolytic and aplastic anemia and some of antituberculosis drugs have being recorded to cause both.[29] Long term exposure to anti-tuberculosis medication increases the risk of adverse drug reactions and toxicity. Isoniazid and rifampicin may directly cause hemolytic anemia, as can pyrazinamide cause sidroblastic anemia.[30] Others have suggested that anemia is seen as part of the clinical manifestation of tuberculosis and as a consequence of a chronic disease. In general, tuberculosis patients have a higher predisposition to develop gastro-intestinal absorption problems, consequently leading to anemia.[30, 31]

CONCLUSION

This study showed that some of TB patients who received standard treatment developed drug induced hematological disorders. In as much as there are other adverse effects of anti-tuberculosis drugs, our study showed that drug induced hematological disorders is still one of the prominent public health problem in the South West Region of Cameroon with agranulocytopenia being the most manifested. Patients with agranulocytopenia have been known to usually have a high risk of optimistic infections and will recommend that the dosage of the patients should be adjusted in the case of drug related as in case of our study.

DECLARATIONS

Ethical Considerations

The ethical approval of the study was sought and obtained from the Ethical Review committee of the Faculty of Health Science Institutional Review Board (FHS-IRB) of the University of Buea with Ref number 2015/321/UB/FHS/IRB. Administrative clearance was also sought and obtained from the South West regional delegation for public health and from the directors of the Buea Regional Hospital annex, the Limbe Regional hospital, Kumba general hospital and Mamfe general hospital after presentation of detailed study objectives and procedures. Written informed consent was gotten from each recruited study participant from 21 years and above with participation being voluntary.

Consent for publication

"Not applicable".

Availability of data and materials

All data generated or analysed during this study are included in this published article and available from the corresponding author on reasonable request for futher information.

Competing interests

The authors declare that they have no competing of interest.

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No extertnal funding was inolved in the study. The study design, collection of data, analysis, interpretation and writing of manuscript was done by the Authors and no influence from any external funder.

Authors' Contributions

EJE, BDPT and MNN planned the study and designed the protocols. BDPT, EJE, JCA and MNN supervised the study including collection of samples, data from the questionnaire interviews and management of collected data. EJE and FBT carried out the laboratory work and administered questionnaires to participants. EJE, BDTP, AOE, OMI and FBT carried out the data analysis and interpretation. BDTP, EJE, AOE and OMI prepared the first draft of the manuscript and all the authors revised the final manuscript.

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List of abbreviations

Antituberculosis drugs - ATD
World Health Organization - WHO
Tuberculosis - TB
Directly Observed Treatment, Short-course – DOTS
Adverse Drug Reaction – ADRs
Pyrazinamide - PZA
Human immunodeficiency virus – HIV
Anti-tuberculosis Treatment – ATT

Drug induced hematological disorder – DIHD
Mycobacterium tuberculosis – MTB
Peripheral blood cells – PBCs
Natural Killer Cells - NKC
Faculty of Health Science Institutional Review Board - FHS-IRB
Statistical Package for Social Sciences - SPSS

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